Journal of
CHRONIC DISEASES

VOL. 4 AUGUST, 1956 NO. 2

OL.
4
956

Original Communications

A FOLLOW-UP STUDY OF TUBERCULOSIS IN STUDENT NURSES

II. Mortality From All Causes in the First Decade After Entering Training

Andrew Theodore, M.A., Anne G. Berger, B.A., and Carroll E. Palmer, M.D., Ph.D.

Washington, D.C.

From the Tuberculosis Program, Division of Special Health Services, Public Health Service

(Received for publication Jan. 28, 1956.)

THERE is little reason to doubt that persons in the nursing profession have in the past been subjected to special risks of contracting serious, often fatal diseases. Intimate exposure to patients with communicable diseases, long hours of hard work, and living conditions that were often far from salubrious almost certainly must have contributed to increasing the risk of death from certain causes.

There is also little reason to doubt that occupational hazards for nurses have changed considerably over the past decades. Serious communicable diseases have become much less frequent, and nurses are thus exposed more to patients with chronic, noncommunicable kinds of illnesses. Working conditions have been considerably improved, as have living quarters; and great efforts are being made in most hospitals to protect both student and graduate nurses from special risks and to provide them with good medical service. It seems pertinent, therefore, to study the causes of death that are now the most important among young women in the nursing profession.

This is the ninth in a series of reports on a study of tuberculosis in student nurses, aided by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association. It was presented at the annual meeting of the National Tuberculosis Association, New York, N. Y., May 23, 1956.

The present paper deals with the mortality experience of a group of nearly 26,000 former student nurses during the past ten years. As might have been expected because of the high physical standards generally set for admission to nurses training schools, death rates in the study population were found to be considerably lower during the period of training and the early postgraduate years than corresponding rates for women of the same age in the general population. However, the rates increased during the period of observation and, toward the end of the decade, death rates from all causes equaled, or perhaps even exceeded, those in the general population. While the number of deaths in the study population was relatively small, the findings for two particular causes are highly significant: the unusually small number of deaths from tuberculosis—one-ninth the number expected—and the prominence of violent causes which, in the later years of the observation period, accounted for nearly 40 per cent of all the deaths. In addition, the frequency of certain other causes of death suggests that young nurses are subjected to greater risks than other young women.

VOL 4 195

THE STUDY POPULATION

In the fall of 1943 the Public Health Service, in cooperation with thirty-eight schools of nursing in the metropolitan areas of Baltimore, Detroit, Kansas City, Minneapolis, New Orleans, and Philadelphia, began a long-range study of tuberculosis in student nurses. Schools in Columbus (Ohio), Denver, Los Angeles, San Francisco, and additional schools in Minneapolis and Philadelphia, joined the program during the next two years, bringing the total number of participating schools up to seventy-eight by the fall of 1945. When the program began in a school, all students enrolled were immediately placed under observation; and examinations were made at regular intervals for early signs of tuberculous infection and disease throughout the time they remained in training. Examinations of the students were discontinued only if they left school, either by being graduated or by dropping out before completing training, or if their school withdrew from the program. Altogether, from the fall of 1943 until the fall of 1949, when the cooperative study program was discontinued, over 30,000 student nurses had been examined regularly, the majority of them throughout their full course of training. The group in the study program was probably fairly representative of young women in nurses training during the 1940's.[1,2]

Late in 1951, the decision was made to do a follow-up study for the specific purpose of determining how many of the former student nurses had had clinical tuberculosis or had died of the disease. It was decided at that time to exclude about 4,700 students from the follow-up: those who had remained in training for less than six months, those who had entered training in the fall of 1949 just before the field work for the study was discontinued, and the few students who attended two training schools for Negroes. No other selective criteria were used. The follow-up population thus consisted of a total of 25,752 white women who had come under observation from four to ten years previously. The average interval between the first observation and the follow-up was just over seven years.

A detailed account has been presented in a previous paper[3] of the methods used to locate the former student nurses and to enlist their cooperation in supply-

ing information needed for the follow-up study. Briefly, an attempt was made to contact each person by mail and ask her to complete a short questionnaire which included, among other things, a question about whether any examination had ever indicated that she might have had or now has tuberculosis. The program was initiated in July, 1952, and by June, 1953, completed questionnaires had been returned by over 95 per cent of the entire group. The follow-up was considered complete in October, 1954, when all but 9 of the 25,752 had finally been located and an answer had been obtained to the questionnaire.

Pertinent information about the study population at the time it came under observation as student nurses and at the time of the follow-up may be summarized here. Nearly 70 per cent of the former student nurses were first placed under observation when they began their nursing training as freshmen and approximately 30 per cent were first observed as upperclassmen; the average age of the students was 20 years when they came into the study and 27 years at the time of follow-up. By that time three-fourths of the group had married, more than four-fifths had completed their nursing training, and all but a small fraction of those who had been graduated had engaged in the practice of their profession for at least one year. The population had also become widely dispersed; some were located in each of the forty-eight states and several hundred were living in United States territories and possessions, and in sixty-two foreign countries.

OL.
4
956

BASIC DATA AND METHODS OF ANALYSIS

A total of 96 of the 25,752 former student nurses were found to have died. The deaths of some had been reported by the training schools before the follow-up program was started; information about the remainder was obtained during the course of the follow-up. Although nine of the former students were not located, it seems unlikely that any deaths have occurred among them, primarily because little difficulty was encountered in learning about the 96 deaths and, also, because the deaths were not concentrated among the last persons to be located. (One of the nine who was not located during the follow-up was, in fact, recently contacted through her application for admission to a school in California.) Each of the deceased has been identified as a former student nurse who participated in the earlier study, and a copy of her death certificate has been obtained.

Basic data for the present study also include a record of when each student first came under observation and when she responded to the follow-up questionnaire; that is, the month and year of the beginning and the end of the observation period are available for each person in the study. In addition, the date of graduation for each student who completed training and the date when each of the 96 died are also available. Thus, person-years of observation may be computed in each calendar year from 1943 through 1953 and, also, in each successive year since the date of first observation for the total population of 25,743. This figure includes both those who completed their training and those who did not, but does not include the nine unlocated cases. For the purposes of the present study it has also been considered desirable to calculate separately the person-years of observation for the 21,442 students who were graduated from training school, the beginning of observation being the month and year of graduation. It

should be noted that person-years of observation of the graduates while they were still in training are included in the person-years for the total population.

Nearly 186,000 person-years of observation were accumulated by the total population and 103,000 by the graduates. The data are given in Appendix Tables A and B: in Table A, the person-years are distributed by age in each calendar year from 1943 through 1953; in table B, by age in each successive year since the date of first observation for the total population and since graduation for those who completed training. The 96 deaths are distributed in Appendix Tables C and D according to the same categories as outlined for Tables A and B. In Appendix Table E, the number of deaths from selected causes are shown for each calendar year from 1943 through 1953. Causes of death for the 96 cases were classified by the National Office of Vital Statistics according to definitions given in the *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death*, Sixth Revision, 1948.

For interpreting the results of the study, the observed death rates and the expected number of deaths and death rates were computed. An estimate of the total number of deaths expected each year was derived by first multiplying the person-years in each age group of a given year by the comparable United States white female death rate for that year.[4] The expected number of deaths for each age group was then accumulated to obtain the total number expected for that year. The number of deaths expected from selected causes of death was derived in a similar manner. Expected or observed death rates were computed by dividing the number of deaths in a given year by the person-years of observation for that year and expressing the result per 100,000 person-years.

RESULTS

Deaths From All Causes.—The 96 deaths which occurred in the total study population from 1943 to 1953 give a rate of 52 per 100,000 person-years. Had the study population experienced the same mortality as white women of the same age in the general population, the expected number of deaths for this period would have been 186, a rate of 100 per 100,000 person-years. Thus the deaths in the study population were about one-half of the number expected.

Among the graduate nurses there were 63 deaths, or 61 per 100,000 person-years as compared with 103 expected deaths, a rate of 100 per 100,000. Deaths among the graduate nurses were therefore about three-fifths of the number expected (Tables I and II).

Quite a different picture is evident, however, from a year-to-year comparison of expected and observed numbers of deaths and death rates. As illustrated in Fig. 1, the expected rates for the total study population (and for the graduates as well) decrease during the early years but show little change after 1949. Such a decrease would be expected; it reflects not only the changing age composition of the population (younger women were being added to the study each year through 1949), but also the general decline in mortality of young white women in this country during the past decade. The slightly higher expected rates for the graduates reflect their higher average age as compared with the study population as a whole.

VOL 4 195

TABLE I. EXPECTED AND OBSERVED NUMBER OF DEATHS IN THE TOTAL POPULATION AND AMONG THE GRADUATES IN EACH YEAR, 1943-1953

YEAR	NUMBER OF DEATHS IN			
	TOTAL POPULATION		GRADUATES	
	EXPECTED	OBSERVED	EXPECTED	OBSERVED
1943	2.0	1	0.1	—
1944	9.9	1	1.1	—
1945	16.3	7	3.4	4
1946	21.1	3	6.8	—
1947	21.7	6	10.6	4
1948	22.7	8	13.5	3
1949	23.3	13	14.9	7
1950	23.7	15	16.6	10
1951	23.2	16	18.1	11
1952	20.2	24	16.7	22
1953	2.0	2	1.4	2
Total	186.1	96	103.2	63

TABLE II. EXPECTED AND OBSERVED NUMBER OF DEATHS IN THE TOTAL POPULATION AND AMONG THE GRADUATES IN EACH SUCCESSIVE YEAR SINCE FIRST OBSERVATION OR GRADUATION

NUMBER OF YEARS*	NUMBER OF DEATHS IN			
	TOTAL POPULATION		GRADUATES	
	EXPECTED	OBSERVED	EXPECTED	OBSERVED
IN YEAR	10.3	2	11.1	2
1	27.5	4	20.3	7
2	27.5	11	17.8	5
3	25.7	10	15.8	16
4	23.4	6	14.2	8
5	20.7	11	10.9	9
6	18.4	19	7.0	10
7	16.1	13	4.0	4
8	10.8	13	1.8	1
9	5.2	6	0.3	1
10	0.5	1	0.0	—
Total	186.1	96	103.2	63

*Since the date of first observation for the total population or the date of graduation for the graduates.

The observed death rates shown in the figure for the total study population, and also for the graduates, are much lower than the expected rates during the early years. Apart from irregularities owing to the small number of deaths, there is an unquestionable rise during the middle part of the period; and, in the last years, the observed rates surpass the expected. Although the differences between expected and observed rates for 1952-1953 are not statistically significant,

there can be little doubt that the pronounced advantages held by the study population during the first years of observation have largely disappeared by the end of the period.

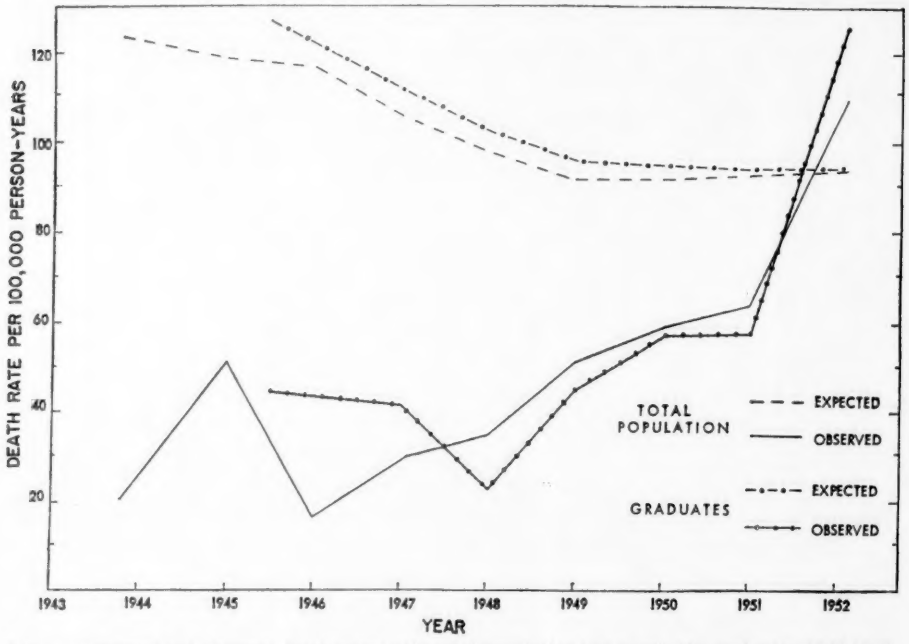


Fig. 1.—Expected and observed death rates in the total population and among the graduates, 1943-1953. *Total population death rates for 1943-1944 and 1952-1953 were combined because of the relatively small number of person-years in the first and last years of the observation period; for the same reason, graduate population death rates were combined for 1943-1946 and 1952-1953.*

Death rates for the former student nurses may also be examined in each successive year beginning with the year of first observation and, also, in each successive year from the year of graduation for those who completed training. Figs. 2 and 3 show that the expected death rates are four to five times higher than the observed in the early years of observation. The expected rates decrease slightly, then rise slowly, whereas the observed rates increase fairly sharply, with the result that the differences between expected and observed rates seem to disappear by the end of the period.

Thus, as might be anticipated, the high degree of physical selection that characterizes young women admitted to nurses training was evident in the results of the present study; death rates from all causes were very low in the study population during the period of training and the following few years. But the effect of that selection became less pronounced during the later years and, by the end of the period, the observed death rates in the study population were about the same, and possibly higher, than the expected rates.

Deaths From Specified Causes.—A remarkable reduction in rates for many of the leading causes of death has occurred in the past decade among the young women of this country.* In Fig. 4 rates are given for the leading causes of death

*In order to have comparable rates for the major causes of death during the years 1943-1953, the United States death rates prior to 1949 were adjusted by grouping the deaths from each cause to conform with the groupings used in the Sixth Revision of the International List of Diseases and Causes of Death.

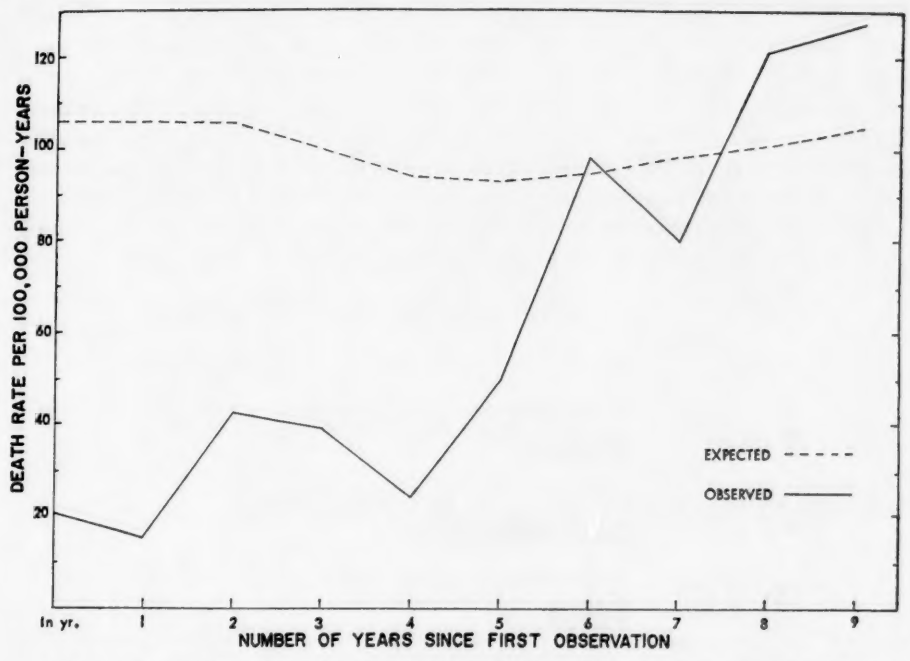


Fig. 2.—Expected and observed death rates in the total population in each successive year since first observation.

Figs. 2 and 3.—Total population death rates for the ninth and tenth years were combined because of the relatively small number of person-years in the tenth year after the date of the first observation; for the same reason, graduate population death rates were combined for the sixth through the tenth years after date of graduation.

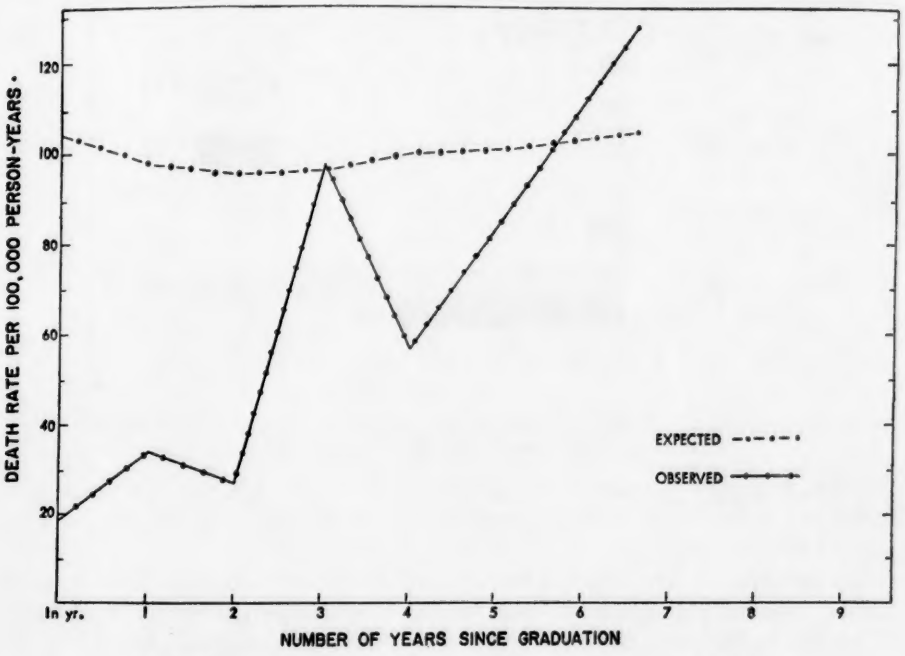


Fig. 3.—Expected and observed death rates among the graduates in each successive year since graduation.

in 1952 and for comparable causes in 1943 in the United States white female population 20 to 29 years of age. Tuberculosis has shown the most dramatic drop, falling from 32 to 5 deaths per 100,000 in the ten-year period. Substantial reductions have also occurred in the death rates for complications of pregnancy, cardiovascular-renal diseases, influenza and pneumonia, and many other diseases. Higher, however, in 1952 than in 1943, are the rates for malignant neoplasms; and rates for violent causes of death—accidents, suicides and homicides combined —have also gained in prominence. Such is the pattern of changes against which the mortality experience of the present study population may be viewed.

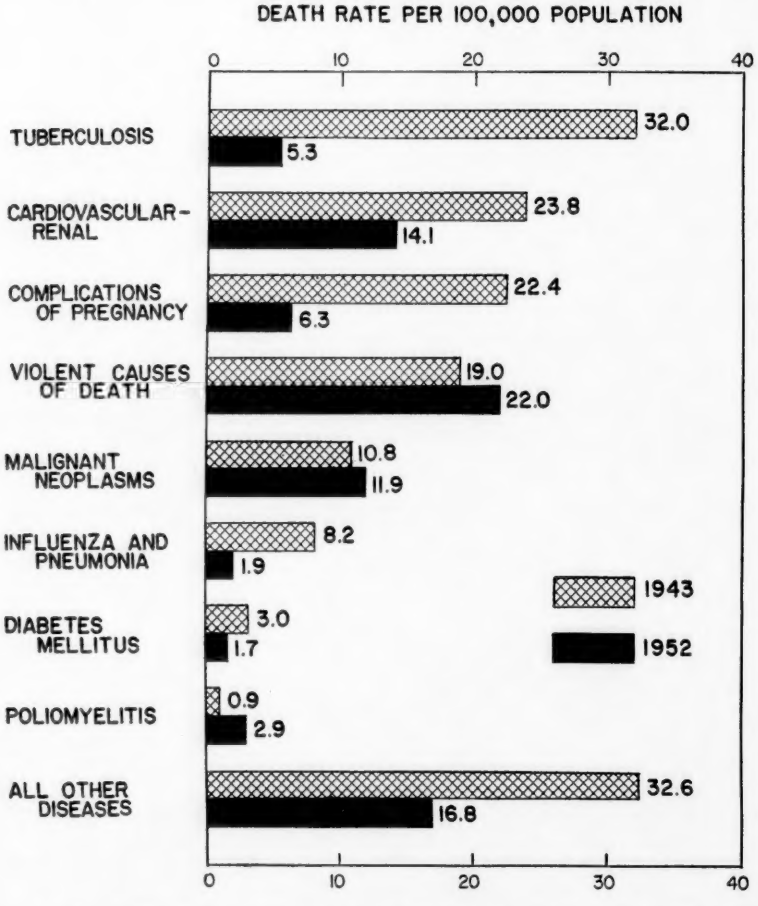


Fig. 4.—Death rates for leading causes of death in 1952 and for comparable causes in 1943 for white females, ages, 20-29, U. S. totals.

The expected and observed number of deaths for the principal causes of death in the total study population and also among the graduates are given in Table III.

Tuberculosis: The largest number of deaths, other than those from violent causes and the cardiovascular-renal diseases, was expected from tuberculosis: 27 women in the study population would have died of tuberculosis had mortality

TABLE III. EXPECTED AND OBSERVED NUMBER OF DEATHS IN THE TOTAL POPULATION AND AMONG THE GRADUATES FOR SELECTED CAUSES OF DEATH FOR THE YEARS 1943 TO 1953, COMBINED

CAUSE	NUMBER OF DEATHS IN			
	TOTAL POPULATION		GRADUATES	
	EXPECTED	OBSERVED	EXPECTED	OBSERVED
Violent Causes of Death	40.5	35	22.1	24
Motor vehicle accidents	*19.1*	*14*	*10.3*	*11*
Suicides	*7.4*	*6*	*4.4*	*3*
Barbiturate poisoning		*7*		*6*
Carbon monoxide poisoning	*14.0*	*2*	*7.4*	*1*
*All other causes**		*6*		*3*
Major Cardiovascular-Renal Diseases	29.9	10	17.4	5
Tuberculosis, all forms	27.0	3	13.5	1
Malignant Neoplasms	21.5	11	13.9	6
Of digestive organs	*2.8*	—	*1.9*	—
Of breast	*2.1*	—	*1.6*	—
Of genital organs	*4.6*	*1*	*3.2*	—
Leukemia and aleukemia	*3.0*	*4*	*1.7*	*3*
Hodgkin's disease†	*2.2*	*3*	*1.3*	*2*
All other	*6.8*	*3*	*4.2*	*1*
Complications of Pregnancy, etc.	17.5	9	9.2	9
Influenza and Pneumonia	6.1	2	3.0	1
Diabetes Mellitus	3.6	2	1.9	1
Poliomyelitis	2.8	7	1.7	5
Hepatitis, infectious†	0.5	2	0.3	1
All Other Diseases	36.7	15‡	20.2	10
All Causes	186.1	96	103.2	63

*Includes all other accidents and homicides.

†Estimates of the expected number for 1943 through 1948 were prepared on the basis of the 1949 U. S. rates.

‡Includes one death from each of the following causes: Asthma, Adrenal Insufficiency, Thrombocytopenic Purpura, Banti's disease, Arachnoiditis, Guillain-Barre Syndrome, Acute Edema of Lungs, Peptic Ulcer, Gastric Dilatation, Postappendectomy, Gastro-enteritis, Cholecystitis with Cholelithiasis, Acute Glomerulonephritis, Polycystic Kidneys, Anoxia.

rates from this disease been the same as in a comparable group of women in the general population. The fact that only three persons—one-ninth of the expected number—died from tuberculosis during the period of observation is one of the most striking findings in the present study.

One student died of miliary tuberculosis in 1948 while still in training; another had dropped out of training in 1945 because of tuberculosis and died in 1949; the third had been graduated in 1943 and died of tuberculous meningitis in 1947. It may also be noted that the first of the three was a positive reactor to tuberculin when she came into training, the second became a reactor while in training, and the third was still a nonreactor at the time of graduation.

About 600 tuberculin-negative students were given BCG while in training, most of them in 1948 and 1949; about 1 per cent of the total person-years of observation were accumulated by these women after vaccination.

Tuberculosis has undoubtedly been an important cause of death in the nursing profession in the past as evidenced, for example, by Heimbeck's findings in Norwegian nurses.[5] Definitive information on the subject in this country is, however, surprisingly scarce. Most of the many studies of tuberculosis in nurses have dealt with the incidence of infection and disease; but mortality, when mentioned, has usually been expressed not as death rates but as the number of deaths in the study group. Data from such studies cannot readily be compared; they are not easy to evaluate and often appear to be conflicting. The number of tuberculosis deaths reported by some authors[6-8] has appeared to be quite high in proportion to the number of persons studied; others[9-11] have reported few deaths and several have expressed the opinion that tuberculosis mortality is low.[12-14] The Prophit Survey,[15] which dealt with tuberculosis among young adults in Great Britain, indicated that tuberculosis mortality rates in nurses were extremely low, lower in fact than in comparable age groups in the general population. The results of the present study give similar evidence. Among over 21,000 graduate nurses only one died of tuberculosis—a rate of 1 per 100,000 person-years where the expected was 13 per 100,000—and that single death occurred in 1947. Although tuberculosis may no longer be an important cause of death in nurses, it may still be an important cause of disease.

Violent causes of death: Violent causes of death—accidents, suicides, and homicides—constitute the leading cause of death in the present study population; more than one-third of the total number of deaths (35 out of 96) were classified in that category, and a striking increase occurred during the study period. As illustrated in Fig. 5, the observed rates from violent causes of death rose from 0 in the early part of the period to about 30 per 100,000 person-years in the last few years. The expected rates, on the other hand, remained below 25 throughout the entire period.

The extremely low mortality observed during the earlier years is in all probability related to the fact that most of the group under observation were in training school at that time and, consequently, living a fairly restricted and probably protected kind of life. The increase in the later years may reflect the greater hazards to which the women must have been exposed after they left school.

Motor vehicle accidents alone accounted for 14 of the 35 deaths from violent causes; overdosage of barbiturates was the next most frequent, accounting for a total of seven deaths; and suicide for six. It is difficult to keep from speculating on the probability that some, or perhaps all of the deaths from barbiturates, as well as the two from carbon monoxide poisoning were, in fact, suicides, even though they were not specified as such on the death certificates. For a graduate nurse (six out of the seven who died of an overdose of barbiturates were graduate nurses) to take a lethal dose of a barbiturate (or any other drug) accidentally is hard to reconcile with her experience in the use and proper dosage of drugs. Similarly, carbon monoxide poisoning might be expected only rarely as an accidental cause of death. If, then, the assumption is warranted that the fatal

barbiturate and carbon monoxide poisonings were not accidental but intentional, the total number of suicides would be 15 rather than 6, thus making suicide the most important single cause of death in the total study population.

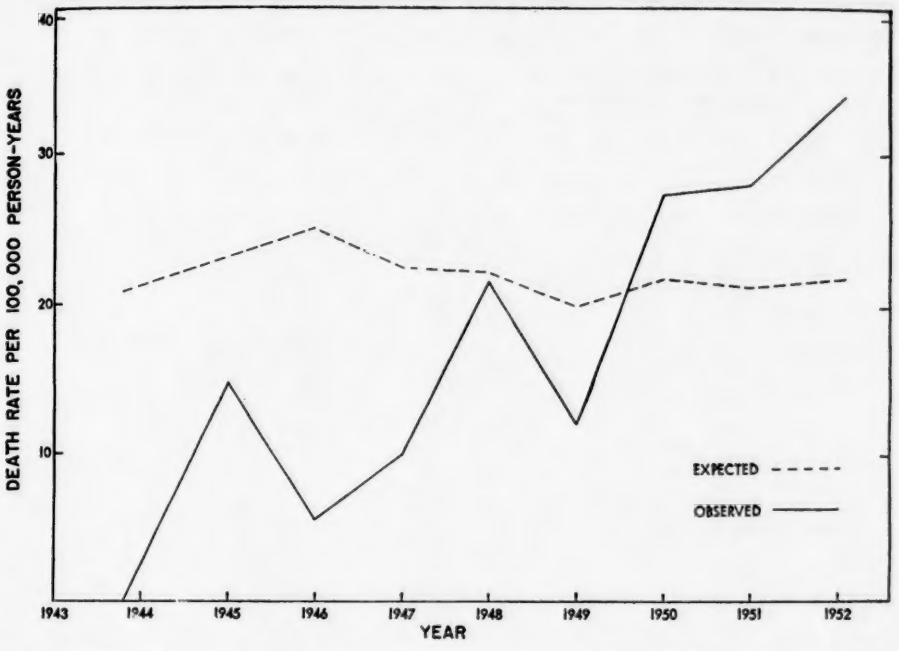


Fig. 5.—Expected and observed rates for violent causes of death in the total population, 1943-1953.

Death rates for 1943-1944 and 1952-1953 were combined because of the relatively small number of person-years in the first and last years of the observation period.

Complications of pregnancy: Seventeen deaths from complications of pregnancy and childbearing were expected in the total population; only about one-half of that number actually occurred. Such a finding, however, might have been anticipated, primarily because a substantial proportion of the person-years of observation was accumulated during the period of training when, ordinarily, obvious restrictions would deter both marriage and childbearing. Those restrictions would not apply after leaving training and, as it happens, there were nine deaths from complications of pregnancy, all among those who had completed their training—a number of deaths equal to the number expected among the graduates.

Another measure of mortality from complications of pregnancy among graduates may be derived from the information presented in Table IV. In this table, the number of married women with designated numbers of children at the time of the follow-up are compared with the number expected if the 1950 United States white female marital and fertility rates for comparable age groups prevailed.[16] Not only were fewer of the graduates married than would be expected (73 per cent as compared with 83 per cent) but those who were married had fewer children. Deaths from complications of pregnancy among the graduates therefore, can, be expressed in terms of the number of children ever born to the group and compared with the corresponding expected ratio. For the graduates one death was observed per 2,200 children whereas the ratio expected was one

death per 3,100 children. Thus, it appears that among graduate nurses deaths from complications of pregnancy were relatively more frequent than expected—a somewhat surprising finding as prenatal and post-partum medical care would, one might think, be more readily available to graduate nurses than to the general population.

TABLE IV. EXPECTED AND OBSERVED NUMBER OF MARRIED WOMEN WITH DESIGNATED NUMBERS OF CHILDREN AMONG THE GRADUATES AND NONGRADUATES AT THE TIME OF THE FOLLOW-UP

STATUS AT TIME OF FOLLOW-UP	NUMBER		PER CENT	
	EXPECTED	OBSERVED	EXPECTED	OBSERVED
Graduates				
Total women	21,379*		———	
Married women	17,811	15,681	100.0	100.0
With 0 children	3,918	4,392	22.0	28.0
With 1 child	5,585	5,246	31.3	33.5
With 2 children	4,837	4,297	27.2	27.4
With 3 children	2,080	1,430	11.7	9.1
With 4 and more children	1,391	316	7.8	2.0
Total number of children	28,282	19,394	——	——
Nongraduates				
Total women	4,268*		———	
Married women	3,513	3,767	100.0	100.0
With 0 children	800	651	22.8	17.3
With 1 child	1,127	1,046	32.1	27.8
With 2 children	942	1,321	26.8	35.0
With 3 children	393	576	11.2	15.3
With 4 and more children	251	173	7.1	4.6
Total number of children	5,406	6,108	——	——

*Excludes deceased women.

For 552 graduates and 107 nongraduates who did not report number of children, an estimate was made on the basis of the corresponding groups who had given information on number of children.

Among the 3,767 married nongraduates who, at the time of the follow-up, had had over 6,000 children, there were no deaths attributed to complications of pregnancy and childbearing.

Malignant neoplasms: The number of deaths from malignant neoplasms in the study population was only about half the expected number. Even though the numbers are small, a breakdown of the data into subgroups reveals several suggestive findings (Table III). No deaths occurred from either cancer of the digestive organs or cancer of the breast, although five deaths were expected. One death was reported from cancer of the genital organs where four to five were expected. This difference between expected and observed cancers of the breast and of the digestive and genital organs would tend to suggest that nurses have certain advantages over the general population in being able to recognize the significance of early signs of such cancers and avail themselves of early, effective

treatment. In contrast, two malignant dyscrasias, leukemia and Hodgkin's disease, were together responsible for seven deaths in the study population when the expected number was five. This finding may reflect the absence of effective treatment for such types of malignancies.

Other specific diseases: Poliomyelitis accounted for a total of seven deaths in the study population where only two or three were expected. In this connection, it may be noted that four of the seven deaths occurred in 1952 among graduate nurses—a year when the rates were also high in the general population. It is also possibly of some significance that five of the seven deaths occurred in the state of Minnesota though not all of them in the same year. The death ascribed to postappendectomy (Table III) occurred three days postoperatively in a woman with acute anterior bulbar poliomyelitis of five days' duration. Thus, while the present results are no more than suggestive, they may indicate that poliomyelitis is perhaps of more importance than has heretofore been recognized as a mortality risk for the nursing profession.

OL.
4
956

Deaths from the cardiovascular-renal diseases were only about one-third as numerous as expected. Influenza and pneumonia, grouped together, accounted for two deaths, as did diabetes mellitus; and in each case the expected number of deaths was somewhat higher—six for influenza and pneumonia, and three to four for diabetes. Infectious hepatitis caused two deaths in the study population and, while suggestive, this finding may only indicate that the diagnosis of hepatitis (as well as other diseases) may have been more precise in the study population than in the general population.

DISCUSSION

A few comments might perhaps be made on the reasons for including in the present study those who did not complete their course of training—nearly one-fifth of the total population.

The physical examinations required of applicants for admission to schools of nursing undoubtedly result in the selection of a group expected to withstand the rigors, both physical and mental, of nursing duties and responsibilities. Many of the poor health risks will have been eliminated by that initial screening process. Yet, during the period of training, additional students will drop out for various reasons, including marriage, illness, and so on. Some may die while still in training, the victims of causes of sudden death such as accidents and acute infectious diseases; others may die after dropping out of school, and in this category are both those who left school for reasons of ill health and those whose illness had its onset after they left training.

A complete picture of the mortality experience of a student nurse population therefore requires the inclusion of all students—those who did not complete their training as well as those who did. For example, had the present study dealt only with graduate nurses, the 33 deaths—about one-third of the total number—that occurred among students who either were still in training or who had dropped out of training would have been missed.

There are also reasons, of course, for analyzing separately the results for the students who completed their training and were graduated. Professional groups, insurance and health agencies, schools of nursing, hospitals, and perhaps other groups may well be concerned with the mortality risks of women who be-

come graduate nurses. Many of them can be expected to engage in the practice of their profession for varying periods of time, either continuously or intermittently, and they are, theoretically at least, exposed to greater health risks than their classmates who were not graduated.

The selective factors that operate to screen the student nurse population both on admission to school and during the period of training are reflected in the mortality experience of the present study group. Death rates were low during the training and early postgraduate years. However, the effects of selection appear to influence mortality only for a short period, or at least the influence of these effects wanes, and by the end of the observation period the death rates from all causes equaled or even surpassed the expected.

The present findings agree with some of the other reports—that the death rate from tuberculosis is very much lower in nurses than in the general population. The present study also points up the great importance of accidents and suicides, which together accounted for more than one-third of all the deaths. Next among the leading causes were malignant neoplasms and cardiovascular-renal diseases, although in each instance the observed number was considerably lower than the expected. Poliomyelitis accounted for seven of the total of 96 deaths, a finding suggesting that this disease may be an important risk for the nursing profession. Deaths from complications of pregnancy were only one-half as numerous as expected for the total population, but for the graduates alone the observed and expected numbers were about the same. Furthermore, in terms of the number of children per death, more deaths occurred among the graduates than would be expected—a surprising finding in view of the greater availability of medical care to nurses than to the general population.

Although nurses undoubtedly are more highly exposed than the general population to communicable diseases, yet in the present study group only a relatively small number of deaths were caused by diseases that could be considered communicable—about one-sixth of the total, which is considerably less than expected. Thus, in so far as the present findings warrant generalization, it would seem that today's young nurses no longer pay a heavy penalty from exposure to communicable diseases. Instead, their greatest mortality risks do not appear to be directly related to their professional services.

SUMMARY

In a study population of nearly 26,000 young women who were placed under observation as student nurses during the years 1943-1949 and participated in a follow-up study in 1952-1953, there were a total of ninety-six deaths from all causes—a rate of 52 as compared with an expected rate of 100 per 100,000 person-years of observation. That the over-all observed rate was about one-half the expected rate can be ascribed largely to the very low rates in the study population during the early years of the observation period when most of the women were in training and the first few years after they left school. Toward the end of the follow-up period, however, the observed death rates were about the same as those in a comparable group in the general population. With regard to specific causes of death, the main findings in the present study were the extremely low death rates from tuberculosis and the prominence of violent causes of death, particularly those from accidents and suicides.

APPENDIX

TABLE A. AGE DISTRIBUTION OF PERSON-YEARS OF OBSERVATION IN THE TOTAL POPULATION AND AMONG THE GRADUATES IN EACH YEAR, 1943-1953

AGE	YEAR											
	Total	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953
Total Population												
Under 20	14,847	610	2,371	3,059	2,722	1,896	2,092	1,821	272	3	1	—
20-24	99,779	897	5,121	9,444	13,218	14,808	14,956	14,404	12,426	8,992	5,205	308
25-29	59,810	68	449	927	1,820	3,248	5,403	8,235	11,436	13,818	13,113	1,293
30-34	8,855	22	117	211	307	410	586	820	1,180	1,913	2,802	487
35-39	1,803	3	29	64	95	125	179	237	297	349	368	57
40 and over	496	1	4	6	14	23	38	59	88	113	131	19
All ages	185,590	1,601	8,091	13,711	18,176	20,510	23,254	25,576	25,699	25,188	21,620	2,164
Average age	24.4	21.0	21.4	21.9	22.4	23.1	23.6	24.2	25.3	26.2	27.2	28.2
Graduates												
Under 20	6	—	—	1	1	—	2	1	—	—	1	—
20-24	46,455	41	668	2,187	4,246	6,716	8,094	7,733	6,680	5,775	4,111	204
25-29	48,255	1	91	393	1,082	2,485	4,519	6,947	9,607	11,516	10,738	876
30-34	7,090	—	15	62	138	268	441	644	979	1,663	2,486	394
35-39	1,383	—	2	18	46	87	136	188	246	296	322	42
40 and over	386	—	1	3	8	17	27	44	68	94	110	14
All ages	103,575	42	777	2,664	5,521	9,573	13,219	15,557	17,580	19,344	17,768	1,530
Average age	25.8	22.6	23.3	23.6	23.8	24.2	24.7	25.4	26.0	26.6	27.2	28.5

Person-years of observation were obtained by accumulating the number of months between the first and last date of observation for each girl and translating the total into years. In most cases the person was not under observation throughout the full 12 months of the calendar year in which she first came under observation; nor throughout the full 12 months of the calendar year in which observation was terminated.

TABLE B. AGE DISTRIBUTION OF PERSON-YEARS OF OBSERVATION IN THE TOTAL POPULATION AND AMONG THE GRADUATES IN EACH SUCCESSIVE YEAR SINCE FIRST OBSERVATION OR GRADUATION

AGE	NUMBER OF YEARS*											
	Total	In Yr.	1	2	3	4	5	6	7	8	9	10
Total Population												
Under 20	14,847	5,183	8,444	1,203	16	1	—	—	—	—	—	—
20-24	99,779	4,036	15,569	22,051	21,682	18,262	12,025	5,534	613	7	—	—
25-29	59,810	359	1,294	1,913	3,207	5,620	9,027	12,453	13,922	8,653	3,161	201
30-34	8,855	101	323	414	525	628	794	1,026	1,374	1,766	1,649	255
35-39	1,803	22	97	130	177	205	223	255	282	242	148	22
40 and over	496	4	12	20	29	47	64	78	91	83	59	9
All ages	185,590	9,705	25,739	25,731	25,636	24,763	22,133	19,346	16,282	10,751	5,017	487
Average age	24.4	20.1	21.2	22.8	23.4	24.0	25.0	26.5	28.0	28.6	29.6	30.8
Graduates												
Under 20	6	4	2	—	—	—	—	—	—	—	—	—
20-24	46,455	9,332	17,125	12,598	6,737	657	6	—	—	—	—	—
25-29	48,255	994	2,935	5,172	8,637	12,383	9,551	5,603	2,420	559	1	—
30-34	7,090	218	457	562	670	779	966	1,071	1,164	936	254	13
35-39	1,383	81	156	172	193	221	209	158	112	65	14	2
40 and over	386	7	25	37	53	64	81	57	38	18	5	1
All ages	103,575	10,636	20,700	18,541	16,290	14,104	10,813	6,889	3,734	1,578	274	16
Average age	25.8	23.2	23.5	24.4	25.8	27.7	28.2	28.6	29.4	31.0	32.8	33.7

*Since the date of first observation for the total population or the date of graduation for the graduates.

The large reduction in person-years of observation from the fifth through the tenth years after the date of first observation or graduation reflects the fact that the population first observed (or graduated) during 1949 could not be observed for more than four calendar years after 1949; those first observed (or graduated) during 1948 could not be observed longer than five calendar years after 1948, etc.

VOL. 4 1956

TABLE C. AGE DISTRIBUTION OF THE DECEASED IN THE TOTAL POPULATION AND AMONG THE GRADUATES IN EACH YEAR, 1943-1953

AGE IN YEAR OF DEATH	YEAR											
	Total	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953
Total Population (Deaths)												
Under 20	1	—	—	1	—	—	—	—	—	—	—	—
20-24	43	1	1	6	2	4	5	12	4	3	4	1
25-29	41	—	—	—	1	2	3	1	10	8	16	—
30-34	10	—	—	—	—	—	—	—	1	4	4	1
35-39	1	—	—	—	—	—	—	—	—	1	—	—
All ages	96	1	1	7	3	6	8	13	15	16	24	2
Graduate (Deaths)												
Under 20	—	—	—	—	—	—	—	—	—	—	—	—
20-24	21	—	—	4	—	2	1	6	3	1	3	1
25-29	32	—	—	—	—	2	2	1	6	6	15	—
30-34	10	—	—	—	—	—	—	—	1	4	4	1
35-39	—	—	—	—	—	—	—	—	—	—	—	—
All ages	63	—	—	4	—	4	3	7	10	11	22	2

TABLE D. AGE DISTRIBUTION OF THE DECEASED IN THE TOTAL POPULATION AND AMONG THE GRADUATES IN EACH SUCCESSIVE YEAR SINCE FIRST OBSERVATION OR GRADUATION

AGE IN YEAR OF DEATH	NUMBER OF YEARS*											
	Total	In. Yr.	1	2	3	4	5	6	7	8	9	10
Total Population (Deaths)												
Under 20	1	—	—	1	—	—	—	—	—	—	—	—
20-24	43	2	3	10	9	3	9	6	1	—	—	—
25-29	41	—	1	—	1	3	2	11	10	9	4	—
30-34	10	—	—	—	—	—	—	1	2	4	2	1
35-39	1	—	—	—	—	—	—	1	—	—	—	—
All ages	96	2	4	11	10	6	11	19	13	13	6	1
Graduate (Deaths)												
Under 20	—	—	—	—	—	—	—	—	—	—	—	—
20-24	21	—	7	3	11	—	—	—	—	—	—	—
25-29	32	2	—	1	5	7	8	6	2	1	—	—
30-34	10	—	—	1	—	1	1	4	2	—	1	—
35-39	—	—	—	—	—	—	—	—	—	—	—	—
All ages	63	2	7	5	16	8	9	10	4	1	1	—

*Since the date of first observation for the total population or the date of graduation for the graduates.

VOL 4 1956

TABLE E. NUMBER OF DEATHS IN THE TOTAL POPULATION AND AMONG THE GRADUATES BY CAUSE OF DEATH IN EACH YEAR, 1943-1953

CAUSE	YEAR											
	Total	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953
Total Population (Deaths)												
Violent Causes of Death	35	–	–	2	1	2	5	3	7	7	6	2
Malignant Neoplasms	11	–	–	–	–	1	–	5	3	1	1	–
Major Cardiovascular-Renal Diseases	10	–	–	–	2	1	1	1	2	–	3	–
Complications of Pregnancy, etc.	9	–	–	2	–	–	–	1	1	3	2	–
Poliomyelitis	7	–	–	–	–	–	–	1	1	1	4	–
Tuberculosis, all forms	3	–	–	–	–	1	1	1	–	–	–	–
Influenza and Pneumonia	2	1	–	–	–	1	–	–	–	–	–	–
Diabetes Mellitus	2	–	–	–	–	–	–	–	–	1	1	–
Hepatitis, infectious	2	–	–	–	–	–	–	–	–	1	1	–
All Other Diseases	15	–	1	3	–	–	1	1	1	2	6	–
All Causes	96	1	1	7	3	6	8	13	15	16	24	2
Graduate (Deaths)												
Violent Causes of Death	24	–	–	1	–	2	2	2	5	4	6	2
Malignant Neoplasms	6	–	–	–	–	–	–	3	2	1	–	–
Major Cardiovascular-Renal Diseases	5	–	–	–	–	–	1	1	1	–	2	–
Complications of Pregnancy, etc.	9	–	–	2	–	–	–	1	1	3	2	–
Poliomyelitis	5	–	–	–	–	–	–	–	–	1	4	–
Tuberculosis, all forms	1	–	–	–	–	1	–	–	–	–	–	–
Influenza and Pneumonia	1	–	–	–	–	1	–	–	–	–	–	–
Diabetes Mellitus	1	–	–	–	–	–	–	–	–	–	1	–
Hepatitis, infectious	1	–	–	–	–	–	–	–	–	–	1	–
All Other Diseases	10	–	–	1	–	–	–	–	1	2	6	–
All Causes	63	–	–	4	–	4	3	7	10	11	22	2

REFERENCES

1. Goddard, J. C., Edwards, L. B., and Palmer, C. E.: Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses. IV. Relationship of Pulmonary Calcification With Sensitivity to Tuberculin and to Histoplasmin, Pub. Health Rep. **64**:820, 1949.
2. Palmer, C. E.: Tuberculin Sensitivity and Contact With Tuberculosis. Further Evidence of Nonspecific Sensitivity, Am. Rev. Tuberc. **68**:678, 1953.
3. Theodore, A., Berger, A. G., and Palmer, C. E.: A Follow-up Study of Tuberculosis in Former Student Nurses. I. Methods of Locating and Obtaining Information from a Study Population of 25,752, J. CHRON. DIS. **3**:499, 1956.
4. National Office of Vital Statistics: Vital Statistics of the United States for the Years 1943-1949 Part I; 1950 Vol. I., Vol. III; 1951-1953 Vol. II. Vital Statistics Special Reports, Mortality From Selected Causes, by Age, Race and Sex: United States, 1943-1953.
5. Heimbeck, J.: BCG Vaccination of Nurses, Tubercle **29**:84, 1948.
6. Badger, T. L., and Ayvazian, L. F.: Tuberculosis in Nurses: Clinical Observations on Its Pathogenesis as Seen in a Fifteen Year Follow-up of 745 Nurses, Am. Rev. Tuberc. **60**:305, 1949.
7. Doran, M. V.: Tuberculosis in Employed Women. Morbidity and Mortality Trends in Relation to Age, Am. Rev. Tuberc. **49**:170, 1944.
8. Louria, M. R.: Pulmonary Tuberculosis in Nurses, New York J. Med. **41**:1573, 1941.
9. Hastings, D. R., and Behn, B. G.: Tuberculosis Among Nurses. A Study of the Effect of Tuberculosis Service on the Incidence of Tuberculous Infection and Disease Among Student Nurses, Am. Rev. Tuberc. **44**:681, 1941.
10. Muschenheim, C., Bunn, P. A., and Lansdown, F. S.: Observations on Tuberculosis Control in a University Hospital, Ann. Int. Med. **24**:968, 1946.
11. Myers, J. A., Boynton, R. E., and Diehl, H. S.: Tuberculosis Among Nurses, Dis. Chest **28**:610, 1955.
12. Connolly, E. C.: Tuberculosis Among Hospital Personnel. New York, 1950, National Tuberculosis Association.
13. Hetherington, H. W., and Israel, H. L.: The Significance of Tuberculous Infection in Employees of Hospitals and Sanatoria, Hospitals **16**:108, 1942.
14. Riggins, H. M.: Tuberculosis Control in Hospital Personnel, Am. Rev. Tuberc. **67**:74, 1953.
15. Daniels, M., Ridehalgh, F., Springett, V. H., and Hall, I. M.: Tuberculosis in Young Adults. Report on the Prophit Tuberculosis Survey 1935-1944, London, 1948, H. K. Lewis & Co. Ltd.
16. U. S. Census of Population: 1950, Fertility, Special Report P-E No. 5C.

VOL 4 195

AGING AND INTELLIGENCE

IRVING LORGE, PH.D.

NEW YORK, N. Y.

From the Institute of Psychological Research, Teachers College, Columbia University

(Received for publication Dec. 17, 1955.)

OL.
4
956

AT THE end of World War I, the War Department released the Army Examination Alpha for use in the testing of intelligence of civilians. To date, the most elaborate application of Alpha was made by Jones and Conrad[4] in their appraisal of the mental ability of the total population in the age range of 10 to 60 years in nineteen New England villages. On the basis of about 1,200 tests, they concluded that the "developmental curve for the total Alpha test may be summarized as involving a linear growth to about 16 years, with a negative acceleration beyond 16 to a peak between the ages of 18 and 21. A decline follows which is much more gradual than the curve of growth, but which by the age of 55 involves a recession to the 14-year level."

This interpretation of their results is responsible for the generalization that intelligence declines from its maximum at, or near, early maturity, i.e., in the twenties. It is my contention that their interpretation was an overgeneralization when it was made, and that today, the results would not demonstrate so dramatic a decline.

Let us look at the Army Alpha itself. Under the pressure of military need, the Army Alpha was developed as a test to be given to groups of soldiers. In general, it was based primarily upon the philosophy and methods involved in the origination of the Binet-Simon Scale and the Terman revision of it. It was fortunate, indeed, that Arthur S. Otis had progressed in the making of his Point Scale sufficiently so that it could be adapted quickly for the making of the Alpha. The Binet-Simon Scale, and all subsequent adaptations of it, arrive at an estimate of a child's or adult's mental endowment through the presentation of a wide range of tasks differing in content, in processes, and in the demands for speed and/or accuracy. The criterion that Binet was trying to estimate was school adjustment; the performances on the tasks should be related to success in learning the facts, skills, and generalizations taught in school. In general, Binet and Simon assumed that the brighter the child seemed to his teacher in school, the greater would be the number of facts, skills, and ideas he would have acquired and, hence, the greater his capacity to learn more such facts, skills, and

Presented before the Thirty-fifth Annual Meeting of the Association for Research in Nervous and Mental Disease, New York, Dec. 9-10, 1955.

ideas in his subsequent education. Thus, Binet and Simon estimated ability to learn in school via the amount of learning that had already been accomplished. The Binet-Simon Scale, thus, included a wide range of tasks that required knowledge of the child's environment. The test questions are a broad mixture of items about word knowledge, arithmetic reasoning, and verbal comprehension, as well as tasks which require fine discriminations, immediate and delayed memory, and the ability to make inferences and generalizations.

The Army Alpha, based as it is upon the Binet-Simon Scale, was built in eight subtests representing a wide range of content and process. The eight subtests were: Oral Directions, Arithmetic Problems, Practical Judgment, Synonym-Antonym, Disarranged Sentences, Number Series Completions, Analogies, and General Information. Each subtest gave credit for speed in performing tasks. The time limits varied from five seconds for a single item in the Oral Directions subtest to five minutes for the entire subtest of Arithmetic Problems.

The evidence is clear that neither the Binet nor any of its successors (such as Army Alpha, the Otis Self-Administering Test of Mental Ability, the Army General Classification Test [AGCT] of World War II, or the recently published Wechsler Adult Intelligence Scale) do measure a single or unitary component of intellectuality. By design, each of these intelligence tests measures an undifferentiated mixture of content, process, and speed. The factor analysts have identified, more or less adequately, over forty different but correlated components in intelligence tests. Thurstone, for example, has identified at least seven major factors or components relating broadly to content, process, and speed. His content factors were named space, number, verbal comprehension, and word fluency; the process factors are called associative memory, perceptual speed, and reasoning. Of course, in a sense, the factor analyst finds in intelligence tests what the test maker had incorporated into the test. For the most part, current intelligence tests emphasize those processes and contents deemed significant for predicting the amount and kind of learning in the school subjects at all levels from the primary grades to postgraduate university education. Some critics of current intelligence tests may assert that the favorite school subjects are like those considered important in the curricula from the 1890's to the 1920's. The narrow scope of most intelligence tests, therefore, did not, or do not, give enough credit to broader objectives of social competence or social intelligence. The ability to get along with people, to empathize or understand them may be as intellectual as the ability to solve a puzzle or to interpret a printed passage. Certainly, no intelligence test designed for appraising the mental ability of adults has as its criterion the successful solution of the range of tasks adult life affords, such as meeting the intellectual requirements of vocation, family life, and economic and social adjustment. The criterion of mental ability needs to be extended to the successful handling of tasks other than those represented by school tasks. Intelligence tests, in the last analysis, represent the orientations of the test maker.

It is not surprising that out-of-school adults make uneven performances on the eight different subtests of the Army Alpha. They are uneven because intelligence is not a single unitary factor; they are uneven because the tests

themselves do not evaluate adequately the full range of competence needed for successful adult activities. Jones and Conrad found considerable differences among the eight subtests. They reported that ". . . In some tests, the adolescents are superior to most of the adults; in others, the adults, on the average, surpass the adolescents. In some tests, the peak of development is reached around 18 years; in others, a slight rise continues well into advanced maturity. . . . It is noteworthy that the tests of information (Test 4, opposites or vocabulary, and Test 8, general information) fail to exhibit a postadolescent decline. Decline is most rapid in Subtests 7 (analogies), 3 (common sense), and 6 (numerical completions)." In specifying the differential successes of adults on the various subtests, Jones and Conrad[4] add the interpretation that the three tests on which declines are greatest ". . . may perhaps be considered, at least on *a priori* grounds, to be the best in the Alpha for the measurement of basic intelligence or intellectual capacity." Jones,[4] at least, has been steadfast in his belief that the two tests on which adults show no loss are the least valid, for he said recently that the "two tests (vocabulary and general information) . . . can be shown to be less valid for age comparisons." [ref. 9, p. 271.] There can be little doubt that more than some of the other subtests, Tests 4 and 8, are measures of "stored knowledge" which most adults constantly use. Stored knowledge, of course, does not remain static or unchanged in adults; it is always being added to and subtracted from. Remoteness from schooling, disuse of content or process, shift in emphasis to accuracy, or even the adaptation of a way of working may influence test results. Disuse of arithmetic reasoning, or an overemphasis upon correctness of numerical completions may be responsible, in part, for some of the lower scores in those tests by people in the later ages.

Basically, the Army Alpha (and tests like it) must be, and is, correlated with the amount and quality of formal education. In World War I, the correlation between Alpha and the highest school grade reached for the native born white draft was 0.65. In World War II, the correlation between AGCT and highest school grade reached also was about 0.65. Schooling makes for a difference in intelligence test scores. The greater the amount of schooling, the higher the intelligence test performance. It is well known that the older adults in the population have had much less formal schooling than those persons born in the last twenty years. Since there is a positive correlation between schooling and intelligence test score, it must follow that the older members of the population necessarily are at some disadvantage not only because of their remoteness from formal schooling but also because they had less of it.

Read Tuddenham has obtained some evidence about the value of formal schooling for intelligence test scores. During World War II, he administered a version of Army Alpha to a representative sample of white enlisted soldiers. The World War II soldiers made a median Alpha score of 104, whereas the median for the World War I draftees was 62. Dramatically, the median for the 1940-45 soldiers was at the 88th centile of the 1917-18 distribution. Of course, World War II soldiers were probably more familiar with objective testing, the tests were given by better trained examiners, and examining conditions were more adequately controlled. The difference, however, was due primarily to the amount of education the two generations of soldiers had received. The

World War II troops had a mean of 10.0 years of formal schooling, whereas World War I's soldiers averaged 8.0 years. Tuddenham[14] interprets the results ". . . as indicating that the present population is superior in mental test performance to the population of a generation ago, and that a large proportion of this superiority is a consequence of more and better education for more people."

How much education a person received depended on when he was born. The census returns for 1950 indicate that the median for years of schooling completed for all persons in the age range 25 to 29 years was 12.1; in the age range 30 to 34 years, 11.6; in the age range 35 to 44 years, 10.2; in the age range 45 to 54 years, 8.8; in the age range 55 to 64 years, 8.4; and among those 65 years and over it was 8.2.[12] Because of the significant correlation of schooling on test score, it is obvious that the relatively limited schooling of the older adults may result in an overgeneralization about intellectual decline, which has less to do with mental ability as such than with the diminished educational opportunities afforded the older people in their childhood and youth.

This possibility that schooling may be reflected in intelligence tests raises a major criticism of the kind of evidence utilized in so-called intellectual decline. Jones and Conrad tested, in their villages, all persons aged 10 to 60 years. They computed the average test performance by single years or by semidecades on the assumption that all individuals in any one age group were just like those in any other age category. The reported data on "years of schooling completed" demonstrates that for one variable at least the assumption is not justified. Indeed, it was less justifiable for the 1920's than for the 1950's, and even less justifiable for rural New England than for the urban United States. The cross-sectional method of getting evidence about the curve of intelligence is seriously prejudiced. Obviously, results from cross-sectional testing can only allow inferences about age differences, not about age changes. Age changes can only be appraised by follow-up retesting of the same population over a length of time. When in succeeding generations the amount of formal schooling, for instance, is the same for the entire age range from 25 to 65 years, then generalization from age differences to age changes may be made somewhat more appropriately. Such equalization, however, is in the future; it was not true of the past.

The effect of schooling on test score, however, can be demonstrated in a cross-sectional study. Tuddenham's is one such study. Another comes from the Psychological Corporation's standardization of the new Wechsler Adult Intelligence Scale. About fifteen years ago, David Wechsler published his now well-known Wechsler-Bellevue Intelligence Scale, a scale comprising eleven subtests. On the basis of the 1939 standardization, Wechsler interpreted the test results for different adult ages as evidence that intelligence was at its maximum at or near the twenties, from which point it declines steadily. At the beginning of this year, the Psychological Corporation issued a restandardized Wechsler Adult Intelligence Scale based on tests given in the 1950's. The manual for the new test shows that the total scaled score increases steadily from the teens to about age 35 years, and that the subsequent decline is very much less than Wechsler projected on the basis of the 1939 standardization.[15] It must be emphasized that the 1950 cross-sectional samples were chosen to be representative of the population of the United States for each specific age-group

tested. Thus, even in the new standardization, the younger age-groups had much more schooling than did the older age-groups. For example, 65 per cent of the 55- to 64-year-olds had eight or less years of schooling, in contrast with 27 per cent of the 16- to 17-year-olds, or 22 per cent of the 18- to 19-year-olds.[16] Even for cross-sectional samples, the generalization that a sharp decrement in intelligence begins in the twenties is not true. The Jones and Conrad 1920 test results reflect the conditions then prevailing; Wechsler's results (which he does not interpret as I do) suggest how timebound the evidence was.

With the passage of time, follow-up studies have become possible. Lorge, in the United States, Husen in Sweden, and Jarl in Denmark have each shown that intelligence test scores are related to the extent of formal education. For example, Lorge[7] retested, with an intelligence test, as adults about 34 years of age, a group of individuals who had been tested just twenty years before. He demonstrated that in the twenty years, in general, individuals maintained themselves in intelligence test performances, but that those who had completed a greater number of years of schooling made greater gains on the second test than their boyhood intellectual peers who had ceased their formal schooling sooner.

VOL.
4
1956

The most important follow-up study, however, was that made by Owens.[10] During 1949-50 he retested 127 males with the same form of the Army Alpha which they had taken as an entrance examination for Iowa State College in 1919. With great care, he shows that the sample retested in 1949 could be considered representative of the entire 1919 applicant group. Over the thirty-year period, the same individuals made a significant increment in the total Alpha score. The over-all gain was accomplished by significant increases in the subtests of Practical Judgment, Synonym-Antonym, Disarranged Sentences, Information, and Analogies. No subtest produced a significant decrease.[10] It is interesting that even for the select sample of college-going youth, the extent of education makes a difference in the extent of gains. The more formal education each individual had, the greater the probability of a gain on the retest. Owens proposed a hypothesis that must ultimately be evaluated, that individuals may have increased their scores on Army Alpha from the freshman to the senior year, and that thereafter possible losses from their senior status occurred between the ages of 20 and 50. Even were the hypothesis to be verified, it would suggest, at the worst, a very slow decrement in intelligence test score to the fifties.

Bayley and Oden,[1] too, retested a superior group over an extended period. They readministered the Terman Concept Mastery Test (consisting of verbal items: synonym-antonym and verbal analogies), at or near the age of 41½ years, to gifted adults who had taken the same test twelve years earlier. They also obtained test and retest scores for the spouses of the gifted for the same time span. For both groups, scores were consistently higher at the second testing, with somewhat larger gains on the synonym-antonym subtest. The Concept Mastery scores are positively related to the amount of education the respondents had had.[1]

The Owens,[10] and the Bayley-Oden follow-up studies are based on select populations of former college students and of previously identified gifted persons.

(It is assumed that the spouses of the gifted are also select by assortative mating.) The Lorge sample was just above the average of the population since the majority had achieved eighth grade graduation in 1919. Birren[2] would argue that the rate of intellectual change with age in the elite 5 per cent of the population would be quite different than for the rest of the population.

Unfortunately, not much evidence is available about the adult status on intelligence tests of children who had been diagnosed as feebleminded or of low intelligence. Muench[8] readministered the same intelligence test battery to eight adults who eighteen years previously had been in a group of 40 boys diagnosed as feebleminded. Seven of the eight gained on the readministration of the 1916 revision of the Stanford-Binet given at or near age 31 years. The average increase in the intelligence quotient was more than 15 points. All eight gained on the Army Alpha, with an average gain of 11 IQ points; all gained on the Porteus maze with an average gain of 24 points. All changes are statistically significant. While it is hazardous to generalize from eight cases, the direction seems to be for maintenance or increase in intelligence test scores.

Don C. Charles[3] retested 24 adults who, as children, had been classified as mentally deficient by two criteria: Binet intelligence quotients under 70 *and* the inability to perform school work satisfactorily. On the Wechsler-Bellevue used as retest, 21 subjects gained on verbal IQ. Basically, verbal performance and full-scale IQ's were higher than the original Binet IQ's. The adults at the time of retest ranged in age from 36 to 49 years, averaging 42 years. Part or all of the gains may be a function of the different tests used. Charles, however, attributes the gain to underestimates of intellectual status in childhood.

The major emphasis of Charles' study was upon current social status of children who had been designated feebleminded. From the evidence he concluded: "Social achievement and/or test scores suggest that about 65 per cent of the subjects who tested low originally, now give evidence of being in the dull-normal or average range. If ability to hold a job, to maintain a family, and not to get involved in lawbreaking is an indication of adult adjustment, then it may be inferred that even the so-called dull may keep, or improve upon, their childhood status." Neither Muench nor Charles suggests a decrement in intelligence over the age ranges they studied. Indeed, Charles, in his summary of the literature about the adult status of children diagnosed as dull in childhood, suggests a fairly bright picture for adults judged mentally deficient in childhood.

The evidence about the adult performances of the mentally dull is, as has been indicated, inadequate. Nevertheless, when coupled with the reports of Owens, and of Bayley and Oden, it allows the broad generalization that adults do not decline in intellectual status when changes in intelligence are appraised by retests of the same individuals. It is reasonable to conclude that intelligence is maintained within the *same* person without significant diminution through the twenties, the thirties, and the forties. Indeed, I would venture that, for the same individuals, there would be little if any loss, on the average, through the fifties and the sixties. Basically, I am suggesting that the cross-sectional method gives a biased estimate curve of intellectual growth, maintenance, and decline (?) because the cross-sectional approach does not correct adequately for the differential educational attainments of young and old adults.

Of course, intelligence tests give credits for the completion of tasks which are an undifferentiated mixture of content, process, and speed. Intelligence test scores in the late teens and in the sixties may be based on different kinds of tasks. For example, Jones and Conrad[4] concluded that "In the sixth decade of life, 40 per cent of total Alpha score is derived from two tests (Test 4 and Test 8); at age 10, these tests contribute only 25 per cent." Factor analysis of intelligence test scores at different ages indicates that the tests measure different amounts of the principal component at different ages. In Spearman's[11] terms, the principal component (which he calls *g*) is the factor that is involved in "the measurements of ability of all kinds, and which is throughout constant for any individual." As estimated, *g* accounts for the variance of test scores in the Bellevue-Wechsler about as follows: at age 9, for 44 per cent; at age 12, 41 per cent; at age 15, 31 per cent; at ages 25 to 29, 27 per cent; at ages 35 to 44, 38 per cent; and at ages 50 to 59, 50 per cent.[6] This may be evidence that in the teens much of the intelligence score comes from credits for speed, at least more than is true for test score in the middle or later years. Spearman,[11] as a matter of fact, on much less evidence concluded that ". . . *g* increases from birth—at first rapidly, then more and more slowly—until somewhere not later than 15-16 years (and perhaps much earlier) its growth definitely ceases. Thereafter, it normally retains this maximum level unaltered right up to the end of life (or, at least, to the onset of senility)."

Lorge has demonstrated that older adults were penalized by *speed* on intelligence tests that were an undifferentiated mixture of power and of speed. He estimated the penalty that "speed" places upon the intellectual performance of adults. He applied a statistical correction for the speed penalty for each year following age 20 years to the data reported by Jones and Conrad. The speed factor apparently accounted for the observed decline in Alpha scores. Lorge's[5] procedure does not prove that there is no decrement; it implies, however, that the inference of mental decline may be a function of the weights given to speed, to process, and to content in intelligence tests designed for school children. Much of the so-called decrement is attributable to the diminished "speed of reaction" or the slower adapted tempo of work by older adults. Certainly, when intelligence is measured in terms of power to perform regardless of speed, ability tends to remain stable for a long-time span after age 20.

In summary, the so-called decline in intelligence does not seem to be evident when the same individuals are retested after ten, twenty, or thirty years. The few follow-up studies allow the hypothesis that adults in their thirties, forties, or fifties will test at least as well as they did in the late teens or early 30's. Follow-up evidence points the direction of significant gains in middle maturity. The gains, for the most part, come from test items with very large components of verbal ability, or *g*, or of "stored knowledge." The follow-up studies suggest, moreover, that increments in test score in middle maturity are related to the recency and extent of formal education.

Cross-sectional studies based on more recent testing in the 1940's and 1950's suggest the so-called curve of intellectual decline was a function of the educational status of the individuals tested. The empirical decline, as reported for cross-sectional samples in the 1940's and 1950's, is much less precipitous and is postponed at least a decade beyond the results for 1920 and 1930. It is reason-

able to expect that if the observed results were corrected for the regression of intelligence test score upon the extent of formal education, the empirical decline would be even smaller. The amount and quality of formal education is but one factor. Adults in middle and late maturity, in our culture, get many other intelligence-maintaining stimulations in their expanded leisure time. Adults, today, have the advantage of more and more transactions with one another and with the ideas and events of the modern world. Easier transportation and enhanced communication by radio, television, and print may postpone or prevent intellectual decline.

The pitfalls surrounding the estimation of the curve of intelligence from infancy to late maturity, of course, are also found in the estimation of learning ability in the years following age 20. No one, so far, has made a longitudinal follow-up study of the amount or quality of the "learning" of adults. It would be interesting to discover if individuals who could have learned a skill, or a language, or methods of solving problems at the age of 20 could do related but different problems at age 40, or 50, or 60. It is my belief that anybody can learn at the middle or later years the same kinds of things he could have learned in the teens or early twenties. The difference in the amount and quality of learning will depend upon the amount of time devoted to learning it. This implies, of course, that a decrement in speed and in sensory acuity may be a concomitant of the physiologic process of aging.

Again, the generalizations about learning ability in older adults are a function of the appraisal of learning performance and the kinds of crosssectional samples tested. Beginning with Edward L. Thorndike's book, "*Adult Learning*,"[13] the experimenters have measured learning in terms of rate; the amount produced per unit time, or the time required per unit amount. It is to be expected that decrements in rate necessarily are related to diminished reaction time or to adapted tempo. When learning, however, is measured in terms of accuracy or just "Can it be learned?" the adult in or past the middle years can and does learn. Indeed, Welford has suggested that older adults frequently can compensate for deficiencies in sensory acuity and reaction time by working more cautiously, by greater effort, or by deliberate slowing down. In his experimental work on skill and age, therefore, Welford has deliberately minimized for his experiments the potential contribution of wisdom in compensating for the physiologic changes that age inevitably brings. In complex tasks involving sensorimotor skills, Welford[17] found that the amount of learning depends upon the extent to which the adult can control his method and his timing. He states: "Where such control can be fully exercised, compensation is likely to occur, but where the performance is narrowly constrained in either the form or timing of the constituent reactions, the compensation will be virtually impossible. It can be readily seen that receptor functions, insofar as they deal with events of external causation impinging upon the subject, are essentially less under his control than effector processes initiated by his own central mechanisms, and therefore permit less compensation for deficiencies of ability, and are likely to break down sooner. Where rigid constraints are placed upon effector processes, . . . effector functions are likely to break down just as rapidly as receptor." Welford, therefore, emphasizes both time, stress, and speed of integrating information in measures of learning. In his experiments, however, although time,

errors, and trials are increased as a function of the age of the subjects tested, basically the subjects could and did learn. Of course, Welford cannot be certain that his older subjects were equivalent to his younger subjects in power, intelligence, education, motivation, and the like. Currently, there is no way by which it is possible to demonstrate the equivalence of cross-sectional samples. Nevertheless, the generalization is reasonable that an older adult can learn at later ages what he could have learned at a younger age if he is allowed to use his wisdom in reducing speed to increase accuracy, or by transferring from earlier acquired skills to new skills. Kay[9] cautions, however, that the older adult may be at a disadvantage in learning a new skill when previous experience is inapplicable. As he puts it, "And the adult's deficiencies here primarily arise, not because any retaining mechanism is functioning inadequately but, rather the reverse, it is holding on too indelibly to what it already holds and is not sufficiently flexible to cope with new data." It is in the area of "transfer of training" that adult learning must be studied. Can "stored knowledge" of skill, fact, attitude, or value act as an obstacle? Will it make for rigid and inflexible approaches to the acquisition of new learning? Whatever evidence there is available suggests that the older adult fails when he perseveres in making irrelevant transfers or when he does not try to transfer from relevant learnings. These failures, however, are not serious in the age range from 20 to 50 years.

Intelligence and ability to learn, while not perfectly correlated, are sufficiently related to suggest that both intellect and performances using it are maintained without significant decrement through early and middle maturity. The imputed decline, to a large degree, is a consequent of thinking by analogy, constrained tests, and a limited concept of what is implied by learning ability.

OL.
4
956

REFERENCES

1. Bayley, N., and Oden, M. H.: The Maintenance of Intellectual Ability in Gifted Adults, J. Gerontol. **10**:91, 1955.
2. Birren, J. E.: Age Changes in Mental Abilities, J. Bus. **27**:156, 1954.
3. Charles, D. C.: Ability and Accomplishment of Persons Earlier Judged Mentally Deficient, Genet. Psychol. Monogr. **47**:3, 1953.
4. Jones, H. E., and Conrad, H. S.: The Growth and Decline of Intelligence: A Study of a Homogeneous Group Between the Ages of Ten and Sixty, Genet. Psychol. Monogr. **13**:223, 1933.
5. Lorge, I.: The Influence of the Test Upon the Nature of Mental Decline as a Function of Age, J. Ed. Psychol. **27**:100, 1936.
6. Lorge, I.: [Review of] David Wechsler, The Measurement of Adult Intelligence, J. Cons. Psychol. **7**:167, 1943.
7. Lorge, I.: Schooling Makes a Difference, Teachers College Record **46**:483, 1945.
8. Muench, G. A.: A Follow-up of Mental Defectives After Eighteen Years, J. Abn. and Soc. Psychol. **39**:407, 1944.
9. Old Age in the Modern World: Report of the Third Congress of the International Association of Gerontology, London, 1954, Edinburgh and London: E. and S. Livingstone Ltd., 1955.
10. Owens, W. A., Jr.: Age and Mental Abilities: A Longitudinal Study, Genet. Psychol. Monogr. **3**:48, 1953.
11. Spearman, C.: The Abilities of Man, London, 1929, The Macmillan Company.
12. Statistical Abstract of the United States: Washington, D. C., 1954, U. S. Government Printing Office.
13. Thorndike, E. L., et al.: Adult Learning, New York, 1928, The Macmillan Company.
14. Tuddenham, R. D.: Soldier Intelligence in World Wars I and II, Amer. Psychologist **3**:54, 1948.
15. Wechsler, D.: The Measurement of Adult Intelligence, Baltimore, 1944, The Williams and Wilkins Co.
16. Wechsler, D.: WAIS Manual: Wechsler Adult Intelligence Scale, New York, 1955, The Psychological Corporation.
17. Welford, A. T.: Skill and Age, London, 1951, Oxford University Press.

THE GENETICS OF AGING

FRANZ J. KALLMANN, M.D.

NEW YORK, N. Y.

From the Department of Medical Genetics, New York State Psychiatric Institute, Columbia University

(Received for publication Dec. 30, 1955.)

VOL
4
195

ONE of the notable achievements of modern medicine has been the gradual extension of the average human life span. At the same time, our problems and responsibilities in this area have necessarily multiplied. It is a remarkable fact that in little more than two decades, from 1930 to 1953, the equivalents of nine years—9.1 years, to be exact—were added to the total life expectancy in this country.[4] This gain, accomplished chiefly by improved control over life-shortening factors, brought the general chance of survival appreciably closer to the potential length of life. However, the given increase has not changed the potential life span as such, nor has it sufficiently enhanced our knowledge of the nature and extent of intrinsic longevity potentials.[22]

In general terms, aging has been defined as a gradual loss of ability to maintain a constant level of physiologic equilibrium. Hence, it is the ability to withstand the ensuing impairment of health that determines survival to an advanced age. This capacity is known to be so variable that the many observed differences from one person to another strongly indicate the operation of gene-controlled phenomena.[14,15] That the potentiality for a long life, derived from a fortunate combination of health-conferring genes, can be modified by adverse life conditions in no way lessens the significance of this fundamental biologic hypothesis.

DIFFERENTIATION OF GENETIC VARIATIONS IN AGING

Genetically, a distinction is made between the effects of gene-specific processes causing premature or other pathologic disturbances in the last sector of the human life cycle, and those of general genetic phenomena which produce differences in basically positive health and survival values.[13] The symptoms observed in the first group of disorders are likely to be the result of one major mutant gene that follows the single-factor type of inheritance.

Seen in the second group of variable patterns of adjustment are gradations in normal aging potentials which result from the interaction of several or many genes and are therefore ascribable to the multifactor or polygenic mode of in-

---

Presented before the Association for Research in Nervous and Mental Disease: The Neurological and Psychiatric Aspects of the Disorders of Aging; New York City, Dec. 9-10, 1955.

heritance. Extreme variations determined in this manner (through the accumulation of short-life genes) are apt to produce deviations from the mean health status of an aging population, which are classifiable as pathologic. Some of these deviations may be so clearly pathologic as to be indistinguishable from either a single-factor type of disturbance or a so-called phenocopy (a nonhereditary variation simulating the phenotype of a mutant gene).

Still another group of minus variations in adjustment to aging is due to gene-controlled deficiency states, physical or mental, which arise before the senescent period but tend incidentally to alter the adaptive plasticity of aging persons. In this category are the major psychoses, specific metabolic or endocrinopathic disorders, and various types of intellectual subnormalcy and emotional instability, including schizoid personality traits, compulsive drinking patterns, and the like.

OL.
4
956

PRESENESCENT TRAITS AFFECTING AGING

Exact genetic information about the manner in which presenescent maladjustment affects adaptability to aging has yet to be obtained. Longitudinal studies are needed to demonstrate how specific traits tend to complicate, or are complicated by, the ordinary phenomena of old age. Since the few studies made in this field have been related largely to chronologic rather than biologic age, present appraisal of changes due to aging can be no more than a gross approximation.

It would be difficult, for instance, to determine whether complications in the later stages of chronic pathologic conditions, such as hypertension or hypothyroidism, arise in the period of senescence by coincidence or as the result of a causal constitutional relationship. In the case of a gene-specific underproduction of the thyroid, the connecting link may be a disturbance in cholesterol metabolism which affects both physical and emotional equilibrium.

On the whole, the impact of the senium may be expected to intensify preexisting maladjustment. Old schizophrenics and mental defectives tend to deteriorate, and alcoholics almost always show a marked decline in tolerance and general resistance. Similarly, pulmonary tuberculosis seems to have become more destructive in later life.[2]

Regarding emotional maladjustment which phenomenologically falls into the involutional period, the relationship between the effect of advancing biologic age and declining adaptability is demonstrated by persons distinguished by a schizoid type of behavior pattern. There is substantial evidence in support of the theory that the schizoid personality structure is that of a heterozygous carrier of the schizophrenic genotype with an inadequate degree of general constitutional resistance.[12] The presenescent traits most commonly associated with this type are rigidity, compulsiveness, and oversensitivity. Along with the cumulative emotional strain arising from increasingly conspicuous signs of aging, these traits tend to lead to painful experiences in interpersonal relationships, gradually overtaxing the adaptive defense mechanisms.

When a psychotic break with reality occurs, its symptoms are characterized by the inability to find constructive avenues for releasing anxiety generated by involutional changes. Etiologically, however, it is obvious that the causes of such an involutional psychosis are multiple and always include a long history

of emotional instability determined genetically. Admittedly, the biochemical correlates of this deficiency in adjustive plasticity are still very much in need of clarification.

SPECIFIC DISORDERS OF THE SENIUM

Similar uncertainties exist with respect to the genetic aspects of those pathologic conditions which are specific to the period of senescence. Sufficient information is not even available regarding the least common and most easily recognizable disorders known as Pick's, Alzheimer's, and Jacob-Creutzfeldt's diseases. Here, gross and relatively circumscribed brain lesions develop so dramatically and prematurely that from a genetic standpoint it would be possible to think in terms of specific disturbances produced by the effect of single mutant genes.[6,10,18]

Theories of simple dominance or recessiveness have been advanced not only for these three special types of presenile brain atrophy, but also for essential hypertension and cerebral arteriosclerosis and the total group of disorders called senile dementia. However, histologically verified family data are still so scarce in this area that it would seem inadvisable to eliminate polygenic modes of inheritance, even in the fairly well-studied groups of Alzheimer's and Pick's diseases. According to Sjögren and his co-workers,[21] the theory of a simple dominant mode of inheritance has been more clearly substantiated in Pick's than in Alzheimer's disease. The observed morbidity rates for the parents and sibs of affected persons are 19 and 6.8 per cent in Pick's disease, and 10 and 3.8 per cent in Alzheimer's disease.

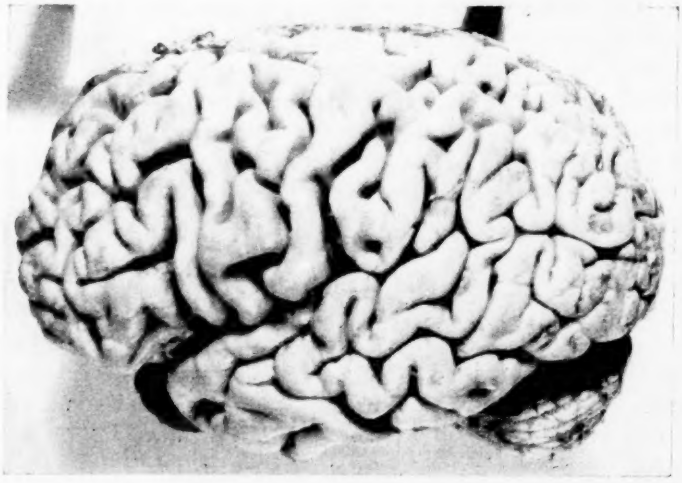
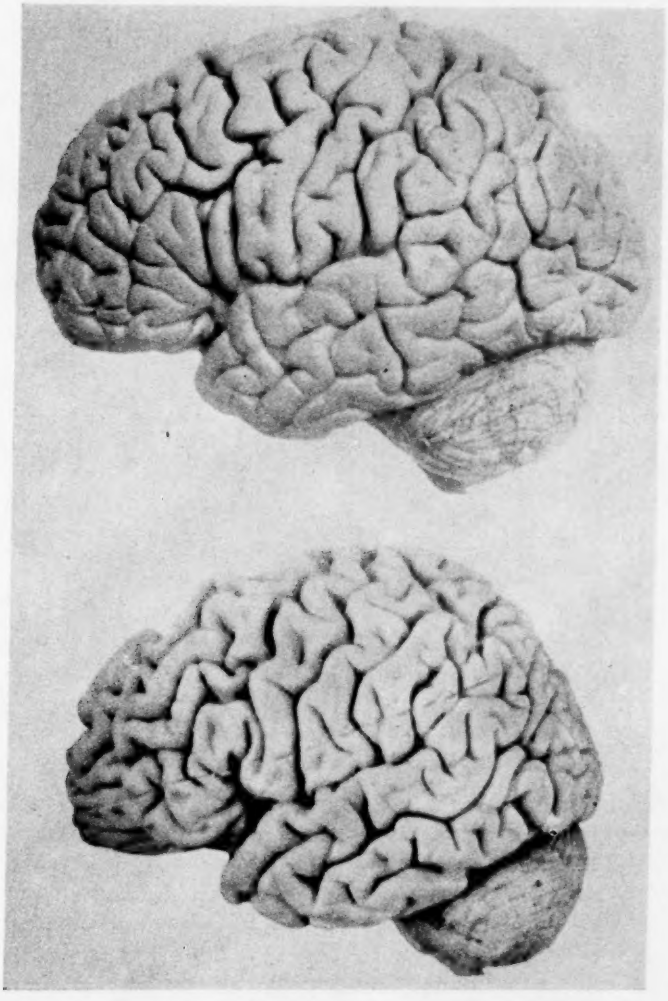


Fig. 1.—Generalized presenile brain atrophy (Alzheimer).

Virtually nothing is known about the gene-specific metabolic disturbances that may be at the root of these two types of early brain atrophy. Conjecturally it may be stated that the given disturbances are likely to differ as much in character as do the structural changes produced by them. It is regrettable that our search for verified twin cases of either type has not been successful, but Dr. Leon Roizin has been good enough to provide some of his material for a brief discussion of the histopathologic differences observed between the two conditions.

In Alzheimer's disease (Fig. 1), the atrophy of the brain, although most pronounced in the temporal and frontal lobes, is rather generalized. On the whole, the narrowing of the gyri and the widening of the sulci are more severe than the common atrophic changes associated with the senium, with or without a history of a senile psychosis (Fig. 2). Microscopically, it can be seen that the early degenerative changes in Alzheimer's disease are quite extreme (Fig. 3). The cytoarchitecture is so disorganized that some areas are entirely lacking in nerve cells.



A.

B.

Fig. 2.—Atrophy of the brain consistent with (*A*) Senescence (age 75) and (*B*) Senile dementia (age 65-73).

Application of the silver impregnation method discloses an abundance of senile plaques, and typical neurofibrillary degeneration is seen in the greatly magnified cell inserted (Fig. 4). Parenthetically it may be noted that these degenerative changes are not argentophilic.

Compared with the atrophic changes observed in Alzheimer's disease, the atrophy of the brain in Pick's disease (Fig. 5) is more circumscribed and usually most severe in the frontal lobes. The postcentral and parietal regions tend to be better preserved. Microscopically, the cytoarchitecture of the frontal lobe may show complete disorganization (Fig. 6). In this instance, there are scarcely any nerve cells left, and certainly fewer than in Alzheimer's disease.

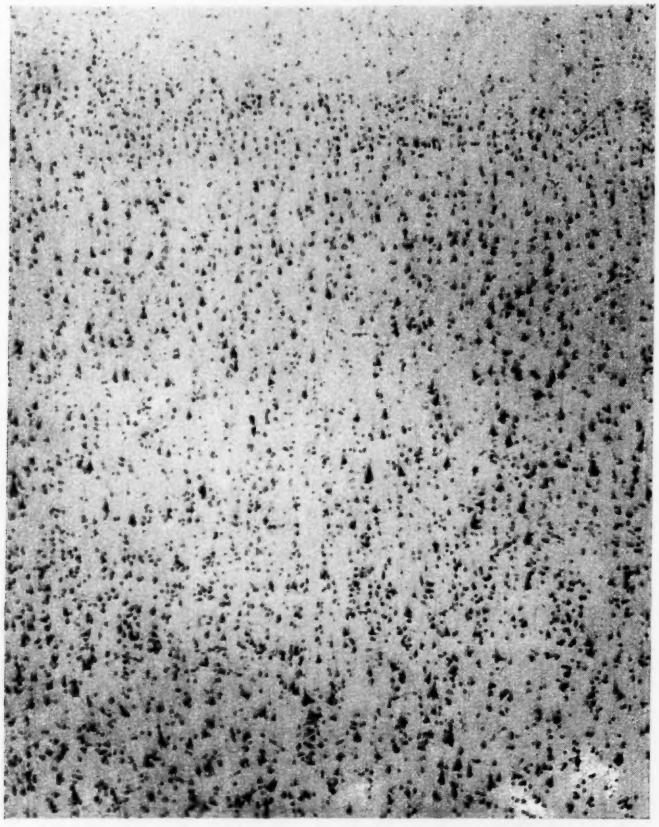


Fig. 3.—Disorganized cytoarchitecture in Alzheimer's disease.

Using Holzer's method for glia fibers (Fig. 7), one finds a marked cortical gliosis, a symptom which distinguishes Pick's from Alzheimer's disease. Greatly magnified, a typical cell described by Pick (Fig. 8) is characterized by an eccentric nucleus and a ballooned appearance of the cellular body.

Within the cell body (Fig. 9), one sees a massive accumulation of lipid material which is highly argentophil in character. This finding and the absence of both senile plaques and neurofibrillary changes are usually sufficient to differentiate Pick's from Alzheimer's disease. In fact, the degenerative processes in Pick's disease are so peculiar that, genetically, they would seem to point to a very specific metabolic disorder which has yet to be identified.

Much additional genetic work is also needed in those disorders in later life in which cerebrovascular changes are the predominant feature. Obviously, arteriosclerotic symptoms are developed much earlier and more severely by

VOL. 4 1956

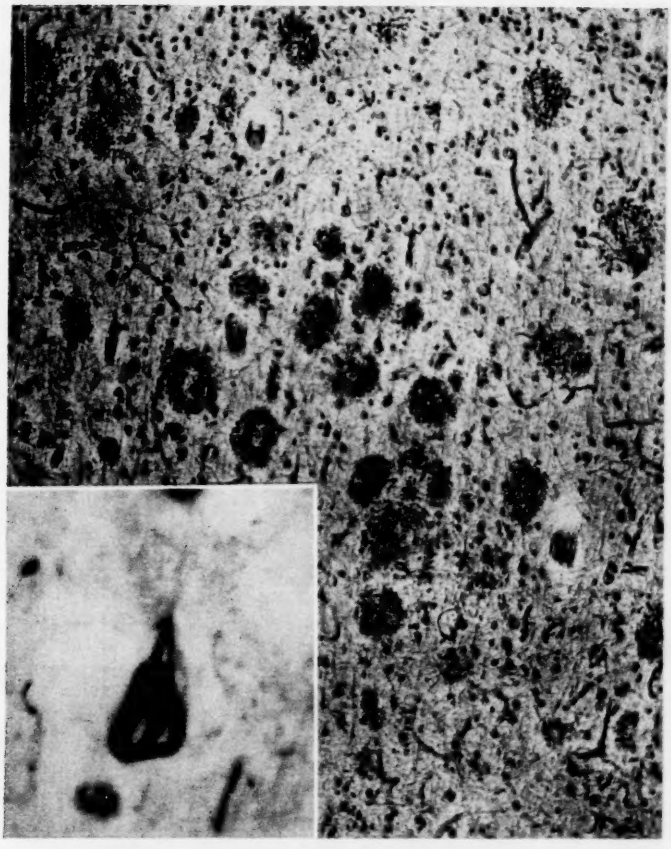


Fig. 4.—Senile plaques and neurofibrillary nerve cell degeneration (inset) in Alzheimer's disease.

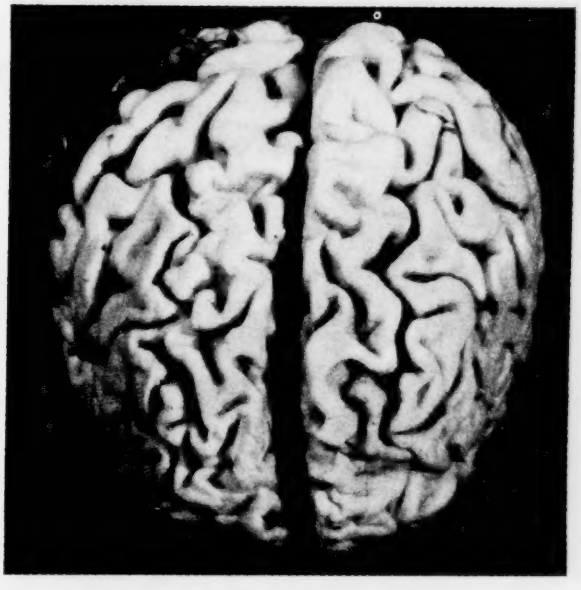


Fig. 5.—Circumscribed presenile brain atrophy (Pick).

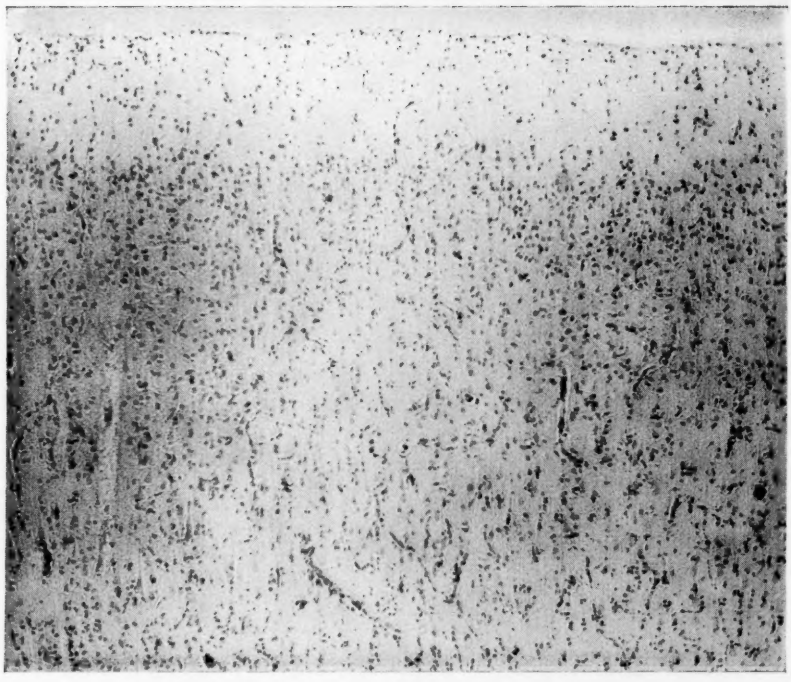


Fig. 6.—Entirely disorganized cytoarchitecture in Pick's disease (frontal lobe).

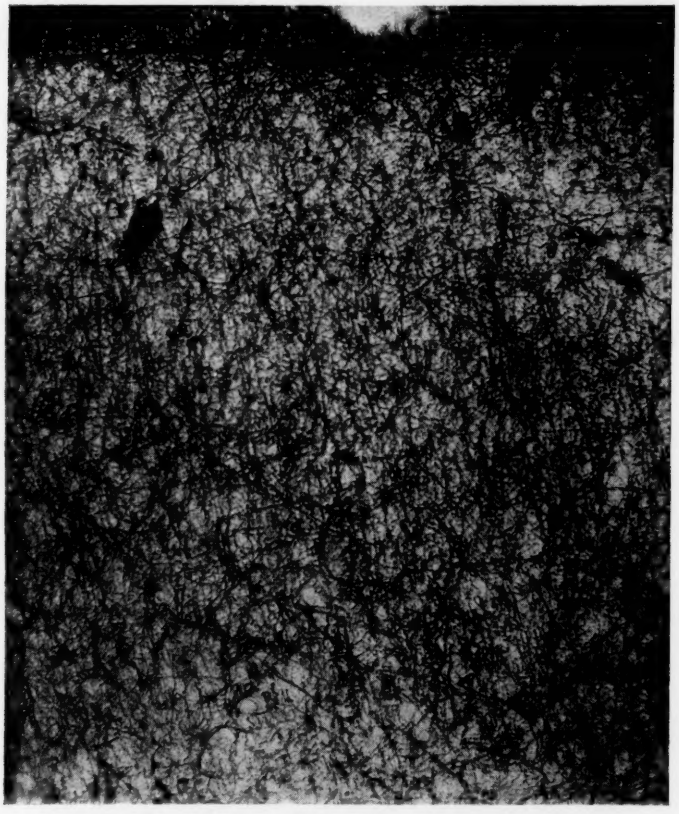


Fig. 7.—Cortical gliosis in Pick's disease.

VOL.
4
1956

some persons than others, and equally variable is the ability to withstand cerebral damage.[1] Clinically, it has also been established that atherosclerosis is a disease in itself and not an ordinary concomitant of aging. In fact, it has been suggested by some investigators that atherosclerosis may actually be two distinct diseases: the first due to defects in cholesterol metabolism or circulatory functions; the second resulting from a breakdown of the structure of the elastic elements in the media of arteries, accompanied by calcification. The increase in deposited calcium has been shown to be associated with an increase in some amino acids, which in turn may be related to the action of elastase, a pancreatic hormone.[9]

Fig. 8.—Ballooned Pick's cell.

Fig. 9.—Accumulation of argentophilic lipid material in Pick's disease.

In any case, it is particularly in the presence of a specific disturbance in lipid metabolism (known as primary hypercholesterolemia) that a familial trend is found toward such pathologic conditions as coronary artery disease, essential hypertension, and cerebral arteriosclerosis.[7,25] Some investigators regard dominant genotypes as the cause not only of a specific predisposition to cerebral arteriosclerosis, but also of its particular localization and frequent combination with nephrosclerosis.[23] However, despite the present evidence for a gene-specific metabolic error being the basic cause of hypertensive disease, many of the etiologic aspects of this serious affliction of the aging are still unsolved.

Equally doubtful is the theory that the total group of senile dementias may be due to the effect of a dominant genotype of low penetrance.[3,19] Either one or two dominant genes have been assumed to be involved, one controlling longevity and one producing the pathologic changes associated with senile dementia. According to the results of our study of aging twin family units, senile psychoses seem more adequately explained by an age-specific intensification of long-existing but minor deficiencies in general emotional adjustment than by a single genetic factor causing a specific type of psychopathology. This theory implies that the genetic components in the etiology of a senile psychosis consist of polygenically determined variations in age-susceptible personality traits, a generally reduced level of adaptive plasticity, and those gene-specific biochemical phenomena controlling growth and decline.

GENERAL HEALTH AND LONGEVITY POTENTIALS

Graded differences in general aging and longevity potentials have been demonstrated by family statistics[5,8,11,20] as well as by twin studies[16,17,24] and are most certainly polygenic in origin. Longitudinal twin data show that compared to the limited degrees of similarity between two-egg twins or ordinary sibs, all measurable similarities between aging one-egg twins are consistently more pronounced, frequently in spite of very different environments. The observed similarities extend to physical and mental signs of aging, social adjustment, intellectual performance, and its rate of decline. The comparative histories of two typical twin pairs may help to illustrate this point.

The twin brothers in Fig. 10 belong in the series of two-egg pairs with very similar life conditions. Reared on a farm, they attended a rural school together, and then became prosperous farmers in the same district. When they were in their early thirties, each married a local girl and each had one daughter. However, despite the similarity of their lives, they developed rather disparate personalities and patterns of aging.

The younger-looking twin on the left, described as prankish, excitable and somewhat extravagant, complained of ill-health for thirty years before retiring at the age of 70. The other twin, who still runs his farm on his own, has always been placid, frugal, and self-sufficient. He takes pride in never having seen a doctor, except for an appendectomy.

As to general intelligence, this twin has maintained a two-point advantage over his brother, with vocabulary scores of 23 and 22 at the ages of 71 and 78. But in this period of seven years, he has deteriorated from a score of 63 to 30 on the tapping test, and from 25 to 17 on the digit symbol test.* The corresponding decline in the twin with the slower aging patterns has been only from 78 to 67, and from 27 to 21, respectively.

The one-egg twins in Fig. 11, on the other hand, are still remarkably alike, both physically and mentally, although their fortunes have differed considerably. Both were employed in factories, married at a young age, and fathered six children each. At 78, one is maintaining a stable home life in a suburban community where he is still active as a cemetery worker. The other neither works any longer, nor does he have a home of his own. For forty years he has been separated from his wife, for whose sake he had changed his religion.

Nevertheless, both twins are in good physical health and blissfully unaware of their equally advanced state of senile deterioration. In the last seven years, their digit symbol scores* have declined at a similar rate, from 13 to 2 and from 11 to 1. Interestingly enough, even the mistakes they make in substituting symbols for digits are precisely the same.

*The psychometric data of this longitudinal test series have been obtained by a team consisting of Dr. Feingold Jarvik, Mr. Arthur Falek, and Mr. Michael Klaber. The detailed results will soon be published elsewhere.

In line with clinical and psychologic observations, it is shown by comparative data on the length of life of senescent twins (Table I) that basic variations in the human life span depend on gene-specific health and longevity potentials.

Fig. 10.—Dizygotic twins at the ages of 23 and 78, respectively.

In those pairs of our sample where both twins died after age 60, the mean intra-pair life span difference continues to be much smaller in one-egg than in two-egg pairs. The present total mean difference varies from 36.0 months in the one-egg group to 74.6 months in the two-egg group of the same sex, and to 106.0 months in dizygotic pairs of opposite sex. In same-sexed pairs, this difference is

about the same for both sexes, despite the shorter life span of the male. It may also be mentioned that one-egg twin partners are more than twice as similar in causes of death as two-egg pairs of the same or opposite sex.

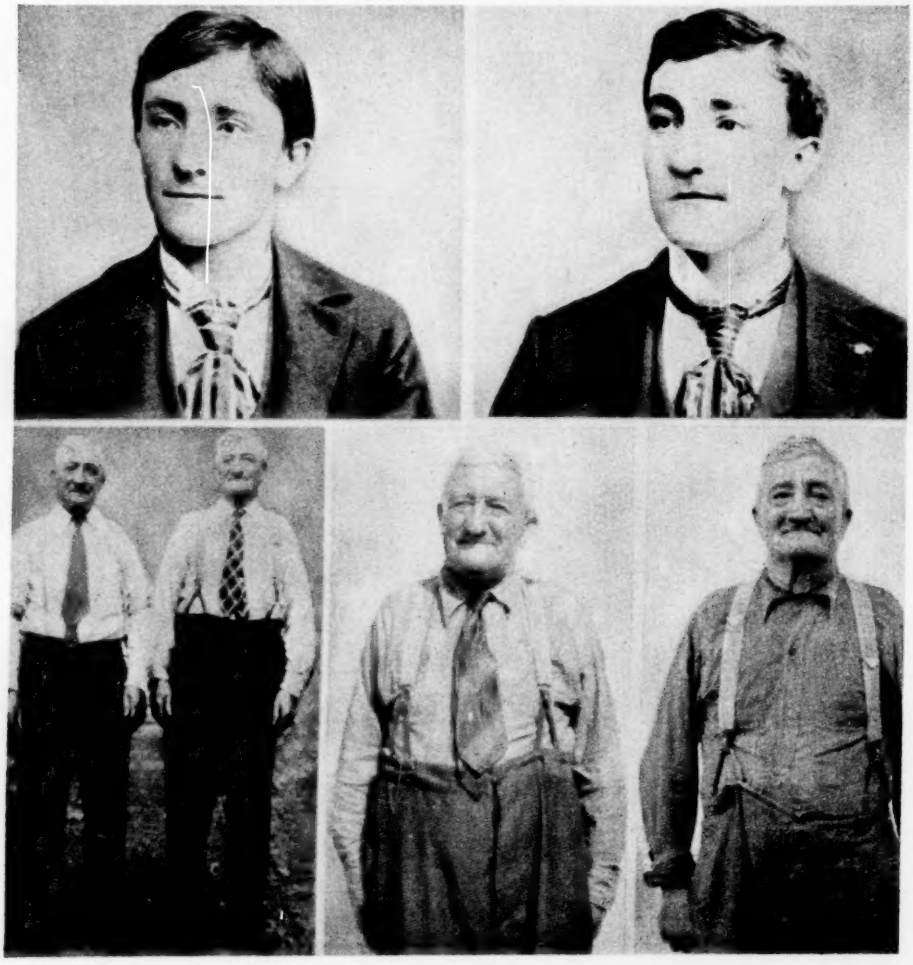


Fig. 11.—Monozygotic twins at the ages of 25, 70, and 78.

The gene-specific basis of longevity and general health potentials in old age is confirmed by a comparison of the life spans of the sibs of senescent twin index cases with those of their parents (Table II). The most striking result of this analysis is the evidence for a direct relationship between parental age and the life span of the offspring. The effect of parental age is independent of sex differences and expresses itself in the life spans of both sons and daughters, irrespective of whether the ages reached at death by the parents are considered individually or together. The comparatively highest mean age levels were attained by twin index sibships when an age of 70 years and over was reached by the mother alone, or by the father alone, or by both parents. There is no evidence for the operation of a sex-linked factor in the inheritance of general longevity potentials.

TABLE I. BIENNIAL MEAN INTRA-PAIR LIFE SPAN DIFFERENCES IN SAME-SEXED TWIN PAIRS OVER 60

	YEAR OF ANALYSIS	NUMBER OF SAME-SEXED PAIRS		INTRA-PAIR LIFE SPAN DIFFERENCES EXPRESSED IN MONTHS		
		ALL PAIRS	BOTH DECEASED	MALE	FEMALE	TOTAL
Monozygotic	1948	237	32	47.6	29.4	36.9
	1950	415	68	42.9	31.2	36.7
	1952	513	76	40.7*	30.7*	35.7*
	1954	513	78	40.7*	31.6*	36.0*
Dizygotic	1948	696	36	89.1	61.3	78.3
	1950	1071	70	79.1	63.2	71.8
	1952	1226	86	79.1*	69.5*	73.7*
	1954	1226	102	69.5*	79.1*	74.6*†

*Significant at 1 per cent level.
†All opposite-sexed pairs over 60: 106.0 months.

TABLE II. EFFECT OF PARENTAL AGE ON MEAN LIFE SPANS OF SENESCENT TWINS AND THEIR SIBLINGS

	MOTHER DIED			FATHER DIED			BOTH PARENTS DIED		
	BELOW 55	55-69	70 AND OVER	BELOW 55	55-69	70 AND OVER	BELOW 55	55-69	70 AND OVER
Male	55.8	58.8	59.6	56.3	57.2	60.2	51.8	61.2	61.4*
Female	64.8	64.0	66.4	63.0	64.3	65.3	62.1	61.7	66.8*
Total	58.5	59.8	62.1	58.5	60.0	61.5	55.9	59.4	62.9

*Life expectancy of the general population born in 1900: males, 48.2 years; females, 51.1 years.

CONCLUSIONS

Based on these findings, the effects of genetic factors in aging may be summarized as follows:

Genetic variations in adjustment to aging may arise from gene-specific traits manifested before senescence, but susceptible to its overstraining effect; or from specific metabolic dysfunctions peculiar to the senium; or from graded differences in general health and survival values. Much additional research is needed in all three categories.

Since genetic phenomena are the cause of many individual differences in the degree of aging, it is inadvisable to approach geriatric problems with the preconceived notion that the adjustive difficulties of the aged are more or less the same for all persons and thus conducive to management by stereotyped methods.

Biologic factors advantageous to adjustment to aging include healthy and longevous parents, the efficacious use of genetic potentialities for physical and mental health throughout life, and the establishment of adequate emotional adjustment before senescence.

REFERENCES

1. Adlersberg, D., Parets, A. D., and Boas, E. P.: Genetics of Atherosclerosis, J.A.M.A. **141**:246, 1949.
2. Chaves, A. D., and Leites, V.: Development of Pulmonary Tuberculosis in Persons Over Forty, Geriatrics **6**:50, 1951.
3. Cresseri, A.: L'ereditarietà della Demenza Senile, Boll. Soc. Ital. Biol. Sperim. **24**:200, 1948.
4. Dept. Health, Education and Welfare: Abridged Life Tables, U. S., 1953. In Official Reports of National Office of Vital Statistics, Vital Statistics Special Report **42**:244, 1955.
5. Dublin, L., Lotka, A., and Spiegelman, M.: Length of Life, New York, 1953, The Ronald Press Co.
6. Essen-Möller, E.: A Family With Alzheimer's Disease, Acta psychiat., Kbh. **21**:233, 1946.
7. Friedman, M., Rosenman, R. H., and Byers, S. O.: Deranged Cholesterol Metabolism and Its Possible Relationship to Human Atherosclerosis: A Review, J. Gerontol. **10**:60, 1955.
8. Gianferrari, L.: Longevità ed Eredità, in Gedda, L. (editor): Genetica Medica, Rome, 1954, Gregorio Mendel Institute, p. 19.
9. Glass, B.: Anatomical and Biochemical Aspects of Heredity in Reference to Atherosclerosis, in National Academy of Sciences: Publication 338, Washington, 1955, National Research Council, pp. 7-13.
10. Jacob, H., Pyrkosch, W., and Strube, H.: Die Erbliche Form der Creutzfeldt-Jakob'schen Krankheit (Familie Backer), Arch. f. Psychiat. Nervenkr. **184**:653, 1950.
11. Jalavisto, E.: Inheritance of Longevity According to Finnish and Swedish Genealogies, Ann. med. int. Fenniae **40**:263, 1951.
12. Kallmann, F. J.: The Genetic Aspects of Mental Disorders in the Aging, J. Hered. **43**:89, 1952.
13. Kallmann, F. J.: Heredity in Health and Mental Disorder, New York, 1953, The W. W. Norton Co.
14. Kallmann, F. J.: Genetic Aspects of Mental Disorders in Later Life. Chapt. in Second Edition of Mental Disorders in Later Life, Kaplan, O. J. (editor): Stanford, 1955, The Stanford University Press.
15. Kallmann, F. J., Aschner, B., and Falek, A.: Comparative Data on Longevity and Causes of Death in a Senescent Twin Population. Chapt. in Analecta Genetica, Vol. 4, Gedda, L. (editor): Rome, 1955, Gregorio Mendel Institute (in press).
16. Kallmann, F. J., Feingold, L., and Bondy, E.: Comparative Adaptational, Social, and Psychometric Data on the Life Histories of Senescent Twin Pairs, Am. J. Human Genet. **3**:65, 1951.
17. Kallmann, F. J., and Sander, G.: Twin Studies on Aging and Longevity, J. Hered. **39**:349, 1948.
18. Malamud, N., and Waggoner, R. W.: Genealogic and Clinicopathologic Study of Pick's Disease, Arch. Neurol. Psychiat. **50**:288, 1943.
19. Meggendorfer, F.: Alterspsychosen. Chapt. in Handbuch der Erbbiologie des Menschen, Vol. V/2, Just, G. (editor): Berlin, 1939, Springer, pp. 1021-1037.
20. Pearl, R., and Pearl, R. De Witt: The Ancestry of the Long-Lived, Baltimore, 1934, Johns Hopkins.
21. Sjögren, T., Sjögren, H., and Lindgren, A.: Morbus Alzheimer and Morbus Pick, Acta psychiat., Kbh., Supp. 82, Copenhagen, 1948, E. Munksgaard.
22. Snyder, L. H.: Human Heredity and Human Deaths. Proceedings of 43rd Annual Meeting of the Medical Section of the American Life Convention, 1955.
23. Søbye, P.: Heredity in Essential Hypertension and Nephrosclerosis, Opera ex Domo Biol. Hum. Hered., Vol. 16, Copenhagen, 1948, E. Munksgaard.
24. Von Verschuer, O.: Wirksame Faktoren im Leben des Menschen, Wiesbaden, 1954, Steiner.
25. Wilkinson, C. F.: Essential Familial Hypercholesterolemia; Cutaneous, Metabolic and Hereditary Aspects, Bull. New York Acad. Med. **26**:671, 1950.

VOL. 4 1956

EXPERIMENTAL PROLONGATION OF THE LIFE SPAN

FRANK POPE, M.D., WANDA LUNSFORD, A.B., AND CLIVE M. MCCAY, PH.D.

ITHACA, N. Y.

(Received for publication Nov. 12, 1955.)

ALTHOUGH Roger Bacon (1214-1292) stated clearly the advantage to man in having a longer potential span of life than most of his domestic animals, little use has been made of this asset in research upon aging or in the study of the diseases of old age.

Some of the reasons that man has failed to make much use of animals in the study of aging are the following:

1. Research in this area is frustrating because the number of variables is large and the work is slow. Hence, graduate students cannot often be interested in such research and the interest in this field does not spread.

2. There are no research institutes for the study of aging where workers can formulate long-time programs and be assured of the same degree of permanency that one finds in other fields such as agricultural experiment station work.

3. Due to variability among individuals as they grow older and are subjected to the hazards of diseases and the accidents of living, research upon aging requires the use of substantial numbers of animals maintained for long periods. Hence such research requires space, which is always at a premium in medical centers, and substantial funds devoted to basic research rather than toward specific diseases.

4. Effective research upon aging requires the cooperative work of groups of specialists if an adequate return is made upon the long-time investment in animal maintenance. Since agricultural colleges usually have the better and cheaper facilities for the maintenance of animals while medical schools have the better laboratories in pathology and physiology, it is important that the two cooperate. However, this is difficult because the physical plants are usually widely separated and the administrative staffs seldom appreciate the advantages of such cooperation.

Finally, after research results are obtained with animals in fields such as nutrition, the obvious paths for confirmation by harmless studies with people are almost entirely blocked to researchers. The place for such tests with people is in the homes for the aged, the prisons, and the mental hospitals. There are

This study was supported in part by Grant No. H-1658 from the National Heart Institute of the U. S. Public Health Service, in part by a grant from the Dental Section of the Office of Naval Research, and in part by a grant from the Rockefeller Foundation.

Presented before the Thirty-fifth Annual Meeting of the Association for Research in Nervous and Mental Disease, New York, Dec. 9-10, 1955.

hundreds of institutions in which active research programs should be in progress dealing with the long-time use of specific foods such as butter, eggs, sugar, or hydrogenated fats or salt, but almost nothing is being done. Such studies would bring new interests into the lives of thousands of people because they would appreciate that they were sharing in attempts to develop ways of better nutrition.

We will continue to make almost no progress in such institutions until (1) we can finance such studies and induce young people to undertake them as their life work and (2) we can relieve institution administrators of enough of their burdens of management so that they can have time to familiarize themselves with methods of research and assume the important administrative roles that are required to make human studies progress.

It is evident that we have the knowledge and techniques in the physical sciences for making great advances in regard to aging, but we lack these assets in social outlook and in institutional administration.

Europe is more backward than America in facilities for long-time animal research; but the Scandinavian countries have done better than we in making use of their institutions in research upon tooth decay and calcium metabolism in old age. At the time of the Physiological Congress in Russia, twenty years ago, there were already paper plans for research institutes upon aging, but if any useful fruit has come from these, it remains little known.

In animal research there has long been some belief that a form of "suspended animation" might prolong the span of life. In the old physiology texts such as that of H. Milne-Edwards published in 1881, one finds attention given to the dehydration of rotifers as a means of preventing the completion and termination of a life cycle. The botanists have long concerned themselves with the length of time that life could be preserved in a dormant seed.

This in turn introduces the possible interrelationships between such phenomena as hibernation, the length of life, and diseases of old age. The possibility that hibernating animals may have unique potentials in regard to life span has come to our attention recently. In the course of retarding the growth of Hamsters by feeding them a low intake of a very high quality diet, Miss Gladys Sperling has observed that the hamsters seem less adversely affected by such retardation than are white rats. Hamsters tend to hibernate during cold weather and rats do not. It is possible that a hibernating animal approaches a grain of wheat in the suspension of animation as a means of lengthening the span of life.

As one tries to analyze the problem of optimum performance of an animal body throughout life, he readily appreciates that there are ideal combinations of such variables as dietary factors or ways of living that must vary for each individual animal in relation to the body it has inherited. At the same time there must be general laws that apply to many individuals and even to many species of animals.

The first of these general laws might seem to be that females outlive males. This has been known in human beings for about two centuries. It is evident in small animal laboratories in which rats or mice are kept for the entire life span. It is not well established for other species because farm animals are seldom kept for the whole of life and no one has bothered to assemble available data upon horses or registered dogs.

VOL. 4 1956

Occasionally, however, in research upon nutrition with white rats the rule is reversed and males outlive the females. After white rats are subjected to long periods of retarded growth by being fed diets excellent in quality but inadequate in quantity, there is no longer a difference between sexes. Hence, such treatment has given the male the same favorable status as the opposite sex in combating the terminal diseases that determine the span of life. Few of us can imagine the changes in our own social structure that would result from equalizing the span of life of the sexes.

Most nutritionists would like to discover a substance, or a combination of substances, that could be fed to an animal with the result that the individual would lead a long, healthy life terminated by a sudden demise. Attempts have been made to discover such effective mixtures of vitamins, proteins, inorganic constituents, and antibiotics but nothing has ever been found to be very effective above certain modest essential basic levels. There may be optimum dietary mixtures but no one has discovered them.

OL.
4
956

There are a number of papers in the literature which give the impression that the life span of some experimental animal such as the white rat was lengthened by feeding it some substances such as calcium salts, vitamin A, or an increased allowance of milk. One needs to examine such data from at least two angles before they are applied in human nutrition. In the first place, one needs to determine if the tests upon the animals such as the rats were valid. Long-time studies with animals are subject to numerous pitfalls, and statistical validity does not ensure that the results can be repeated. Repetition is essential. In the second place one must always ask if the studies with test animals were sufficiently similar to conditions found in man that application is justified.

If we examine the state of our knowledge in regard to the use of experimental animals in the study of diseases of old age and span of life, certain facts emerge.

First, we know that animals such as the white rat grow old and die within a period of two years with many of the terminal diseases of man. Thus, after two years, old rats have fragile bones, decayed teeth, weakened lungs, diseased kidneys, and tumors, but seldom do they show much evidence of cardiovascular diseases.

Next, we know that we can extend the life span and modify the terminal diseases of old age in the white rat by retardation of growth. This result is certain and has interest because it teaches us that we need not face frustration in the field of animal research in longevity.

In the choice of research animals one needs to consider their specific diseases. Of species available today the dog seems the nearest to man. The rat has many assets but its chief liability is bronchiectasis. There is some hope that this disease may ultimately be brought under control and hence improve the usefulness of rats for old age research. The recent progress of Sims and Berg gives hope of prevention or control of this disease in rats. Today every long-time study of rats, whether it concerns reproduction, pharmacology, toxicology, psychology, or endocrinology, is faced with results subject to profound modification in the latter half of life because of the high incidence of pulmonary disease.

In contrast to the white rat, the dog seems to have lungs that function quite well in old age. The lungs of hamsters also seem more resistant to disease during old age than are those of rats. Furthermore, hamsters tend to live slightly longer than rats and to develop forms of arthritis that are worthy of intensive study.

In experimental animals the best way to extend the life span is through partial starvation. This is effective if started even in middle life. However, it is most effective if started with very young rats so that growth is retarded. The normal span of life for the white rat has a mean value between 500 and 700 days; but it is easy to produce substantial numbers of rats that are over a thousand days of age and a few that exceed 1,400 days by keeping them underfed for much of life, upon diets of very high quality. Such procedures of underfeeding profoundly modify terminal diseases. This was observed by Moreschi[1] about fifty years ago when he found he could not transplant tumors into underfed mice. Too little attention has been given to this basic problem of why the internal environment becomes unfavorable for the development of tumors when rats or mice are fed diets rich in all essentials but inadequate for the body in terms of energy sources.

Under such conditions the body probably burns part of its essentials as fuel while the minimum amount of such materials as vitamins and essential amino acids is used to keep living cells functioning. Both the late C. M. Jackson of Minnesota and L. B. Mendel of Yale had some insight into these interrelationships between retarded growth and length of life in white rats. However, they did not design extensive experiments to test their concepts.

When the life of an experimental animal is extended by means of retarded growth, part of the body seems to age at a regular rate. Thus, the bones grow old and fragile although they increase in size after the retardation is ended. Chronic diseases afflict the animals more slowly than normal. The hair and skin retain much of the appearance of youth.

When white rats are allowed to grow at normal rates but are fed diets that differ in type, it is possible to have the same incidence of diseases in old age and the same mean span of life but to have very different conditions of some organs. Thus, if rats are fed nothing but diets of mineralized fresh milk, the teeth remain free of decay until the end of life. When life ends in such animals the bones are also denser than in animals fed mixed diets. Thus, parts of the body may change but the over-all deterioration from diseases remains the same.

Most of the secrets of extended life from the retardation of growth remain to be unravelled.

During the past year we have made a new use of retarded growth to study aging of rats combined in parabiotic union. Nearly a century ago, French physiologists initiated studies of white rats united in parabiotic unions so that they shared most of the circulating fluid through capillary circulation. In exploratory studies we first prepared two pairs of rats with the help of Dr. B. F. Kamrin. One of these pairs survived for a period of 527 days, which is equal to about 53 years in the case of man. We killed the pair at this age because one had developed what seemed to be a chronic bladder infection. This indicated that such pairs could survive into relative old age.

During the past summer the following combinations of animals were united by Dr. Frank Pope: (1) litter-mate rats, aged 2 to 3 months; (2) non-litter mate rats of the same age; (3) litter-mate hamsters; and (4) combinations of rats of widely different ages.

Seventeen pairs of the last were prepared and sixteen were alive in mid-October after the operations had been performed in July and early August.

The mean age at the time of operation for the older members of the pairs was 261 days while that for the junior members was 43 days. On Nov. 11, 1955, the seniors of the pairs had a mean age of one year. The mean difference for members of the pairs is 218 days. This age difference represents about one-third of the span of life of a normal rat or about an equivalent of 22 years for man.

VOL.
4
956

Fig. 1.—Parabiotic union between young and middle aged rats, made when animals were 60 and 300 days old, respectively. Sixteen of these pairs are still alive six months after the operation when the older of each pair was in the last third of the normal life span.

To prepare these parbiotic unions, special techniques were used in preparing the animals to reduce the surgical risks to a minimum. In the first place a succession of litters was produced using the same dam and sire or a closely related sire. Thus, one had rats of different ages from the same parents. In order to have rats of the same size at the time of operation the older rats were retarded in growth and hence were only equal in size to infant rats while in age they were equivalent to adults.

If one compares these rats to men, one can say that it is equivalent to uniting a 4-year-old boy and a 26-year-old man.

Some observations in making these unions were first the severe loss of hair which lasted from two to four weeks. One may ask if this is a reflection of emotional disturbance. In the next place some of the older rats in the combination tended to attack their younger mates and inflict severe injuries upon the head. The anesthesia provided special problems because these rats of two different ages had different requirements even though the bodies had the same weights.

Both sexes have been used in these parabiotic unions between animals of different ages, but not opposite sexes. This needs to be attempted in time to determine if the female in a pair can exert her favorable influence upon the span of life.

One problem that has been encountered in this work is a condition which has been much studied especially by the Germans. This is called parabiosis disease. One of a pair seems to drain the nutrients from the other, with the tail and ears becoming very blanched in the donor while the other has deeply pigmented tail and ears.

It has long been believed that rats retarded in growth accelerated their growth rates when allowed adequate food. This was anticipated as a source of difficulty in making these parabiotic unions, but no evidence has been found that the pair of very different ages grow at unequal rates.

Parabiotic unions between young hamsters of the same age have proved satisfactory. Since the hamster seems relatively easy to retard in growth, it may prove more satisfactory than the rat for union of animals of different ages.

Man has it within his power to modify profoundly the life spans of animals and the diseases that accompany their aging.

VOL 4 195

REFERENCE

1. Lansing, A. I.: Cowdry's Problems of Aging, ed. 3, Baltimore, 1952, The Williams & Wilkins Co., p. 195.

REHABILITATION OF NEUROLOGIC DISORDERS IN THE ELDERLY

HOWARD A. RUSK, M.D.*

NEW YORK, N. Y.

From the Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center

(Received for publication Jan. 5, 1956.)

OL.
4
956

THROUGH the years, the neurologist has been considered by his colleagues to be the great master of finite diagnosis, a skill that has required not only the most complete knowledge of neuroanatomy and neurophysiology, but infinite patience and skillful deductive reasoning. In the past, however, a great number of neurologic diseases were considered to be hopeless once the diagnosis was established, for the etiology was unknown and the therapeutic tools were few and far between.

Although many neurologic conditions are still enigmas, today the attitude has changed. Even though there are but few specifics, the neurologist recognizes that many of his patients can be materially helped with the tools of modern rehabilitation. Leadership in the field of neurologic rehabilitation has come from both the neurologist and the specialist in rehabilitation. There are numerous examples of substantial, even dramatic, results where these tools have been vigorously used.

Soon after World War II, such a program was inaugurated at the Veterans Administration Hospital in Minneapolis for 130 chronic neurologic patients, all but two of whom were veterans of World War I and many of whom had not been out of bed in ten years. After nine months of rehabilitation, 25 had left the hospital and were employed and 40 others, capable of light work, had been discharged to their own homes. Of those remaining, 30 were ambulatory and undergoing advanced rehabilitation, and 25 were capable of some self-care. All but ten of the group had shown some worthwhile, permanent improvement.[1]

Rehabilitation is a teamwork job, not only in name but in operation. In our own services at the New York University-Bellevue Medical Center, the Physical Medicine and Rehabilitation Service works hand-in-hand with the Neurological Service exchanging residents, joining in common rounds, and participating in patient seminars together. All in all, it has been not only a pleasant, but a fruitful relationship. Procedures and techniques have been established that have aided both services in helping the patient and also his family and the community.

Presented at the Association for Research in Nervous and Mental Diseases, Dec. 10, 1955, New York, N. Y.

*Professor and Chairman, Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center.

The subject of our discussion is that of rehabilitation of the elderly patient. In the rehabilitation management of the elderly patient, the procedures are the same as for younger patients; it is only the tempo that is different. Hemiplegia is an excellent example.

HEMIPLEGIA

One of the most significant disabilities in terms of the numbers of patients seen by neurologist is the patient with hemiplegia, usually the result of brain damage following thrombosis, embolism, hemorrhage, or trauma. There are no definitive statistics available on the number of hemiplegics in the United States, but estimates have been as high as 1,800,000.[2]

Some idea of the magnitude of the problems may be gleaned from the fact that "stroke" is listed as the third major cause of death in the United States, ranking behind only "heart disease" and "cancer." Even so, the majority of patients sustaining a stroke of apoplexy do not die from the initial insult. Instead, they improve to a greater or lesser degree, and often live a number of years despite their residual disabilities.

The diagnosis is not difficult but in the past, unfortunately, the medical attitude toward the hemiplegic has been one of hopelessness and passive acceptance. Such patients in municipal hospitals and chronic disease institutions have always posed serious disposition problems and have crowded the few nursing homes and institutions for custodial care. Usually, they remain in general or chronic hospitals, receiving little or no definitive care or the rehabilitation services that might permit them to leave the hospital, or to be referred to less expensive and more suitable facilities. In a recent study of 95 unselected "chronic custodial" cases of which 36 were hemiplegic, it was found that only 7 of the 95 were in need of continued hospitalization.[3]

In the hands of the physician trained in rehabilitation and the rehabilitation-minded neurologist, the hemiplegic is not a lost cause and 92 per cent of properly selected patients can be taught ambulation, self-care, and urinary and fecal continence in an average of six to eight weeks. In addition, 30 per cent of these can be taught to do gainful work, usually in fields related to previous work experience. Further evidence of the value of dynamic rehabilitation services has come from a carefully controlled study in which objective quantitative analysis of comparable groups of patients indicated that a retrained group demonstrated over 130 per cent more gain in activities of daily living than did an untrained group.[4] The return of range of joint motion and muscle strength were also more pronounced in the retrained group, although the increments were not so striking as in the activities of daily living.

In training the elderly hemiplegic, it is important that in the early weeks of the disability, as much of the training as possible be done at or around the bed, for in this period there is still localized edema with continuing confusion. Even a move toward the end of the ward can on occasion be a confusing and disturbing experience. Here again, the general rules for the management of the elderly patient must be fitted to the rehabilitation training program.

The objectives of a program of rehabilitation for the hemiplegic patient are: (1) to prevent deformities, (2) to treat deformities if they occur, (3) to retrain

the patient in ambulation and elevation activities, (4) to teach him to perform the activities of daily living and to work with the unaffected arm and hand, (5) to retrain the affected arm and hand to its maximum capacity, and (6) to manage facial paralysis and speech disability, if present.[5]

The ordinary spastic hemiplegic, when lying in bed, holds the upper extremity in abduction and internal rotation, with the elbow, wrist, and fingers of the affected part in a flexed position. The affected lower extremity is usually flexed at the hip joint; the knee is flexed and the ankle is plantar-flexed and supinated.

If an active program is started within a few days following the cerebrovascular accident, there is no need for any special procedures to protect the affected limbs. If, however, the patient must remain in bed for a period of time, procedures must be instituted to prevent deformities.

A posterior half-shell lower extremity splint is used to prevent shortening of the heel cord. A pillow in the axilla and sandbags laterally will prevent abduction and rotation of the shoulder joint, a frequent residual deformity in hemiplegia. Passive movements of the arm in abduction, external rotation, and in the overhead position should be performed several times a day to prevent a "frozen shoulder."

The principal deformities that may occur are a "frozen shoulder" and short heel cord. The use of heat and massage to the arm and shoulder are of value in preparing the part for stretching. Passive movements of the shoulder are useful in increasing the range of motion.

The use of pulley therapy to prevent shoulder ankylosis will also aid in the development of reciprocal patterns in the upper extremities. This can easily be managed with the use of a modification of an overhead frame, a "window" pulley, and a length of clothesline. Experience has shown that the relative return of function in the affected arm is usually less than in the involved leg. The reasons for this, however, remain obscure. Coordination exercises may be helpful but emphasis should be placed as early as possible on the use of the unaffected arm; this is especially true of the relatively young patient. In addition, a triangular arm sling should be used to elevate the affected arm. This is of aid in minimizing localized edema and in preventing shoulder subluxation.

A short heel cord seldom requires operative procedures. The heel cord can usually be lengthened by means of stretching and a short leg brace with a 90- to 110-degree stop at the ankle to maintain the gains made by stretching and ambulation.

Flexion and extension movements at the hip and knee can usually be performed by the spastic hemiplegic subject who is started on early ambulation. When, however, the hip and knee are flexed, as in walking, the foot dorsiflexes and supinates. The patient is usually afraid to place the supinated foot on the floor because of instability. To prevent this, he walks with a fixed knee joint and circumducts the lower extremity. This is a slow, awkward gait and, if used for a period of time, the patient develops a pattern of walking that is cumbersome, fatiguing, and difficult to correct.

A double bar, short leg brace with a stirrup attachment, 90-degree ankle stop, and a supinator "T" strap should be prescribed to prevent plantar flexions and supination of the foot and give the patient confidence so that he will flex his knee and hip. With the brace, and a cane in the unaffected hand for balance, most hemiplegics soon learn to walk unassisted.

As a return of function in the affected upper extremity is usually very slow, it is essential to teach the patient to care for his daily needs with his unaffected arm.

A right hemiplegia in a right-handed person is an especially serious disability because of the sensory and motor aphasia and the lack of skill in the left hand to perform the activities essential for daily living. The training of the left hand should be started early, as the patient must become left-handed if he hopes to care for his daily needs. Simple tasks in eating and dressing should be started. Left-handed writing must be practiced as this is an important means of communication, especially when speech is affected.

VOL. 4 1956

Training of the affected arm is started while the patient is developing one-handed skills with the unaffected arm. If the arm is flaccid, a re-education program similar to that used in poliomyelitis should be started. Many of these patients have a complete return of function if the muscle re-education is given carefully over a long period of time in conjunction with coordination exercises.

The fingers of the spastic hemiplegic patient are most difficult to re-educate for useful purpose. If adequate function is attained, it takes a great deal of time and concentrated effort by both the patient and the therapists.

In the rehabilitation of the hemiplegic, it is readily apparent that numerous factors will determine the degree of results obtained in ability to perform the activities of daily living. Some patients will achieve a surprising degree of recovery of function; others will be left with varying degrees of permanent residual disability. Even with these latter patients, however, much can be done with the use of simple assistive devices that will enable them to perform many acts of daily living either independently or with a minimum of assistance from another person. Such devices should be used only when necessary, and, before a device is given to a patient, retraining in the activity is a necessity.

One of the most difficult problems in the management of the hemiplegic is the problem of aphasia. It is extremely important for the physician to explain both to the patient (as soon as he is conscious) and to his family what aphasia is and why the patient is unable to speak. Simple as such a procedure is, it is commonly overlooked.

This should be done as soon as the patient has recovered consciousness and aphasia is noted, in order that his fear of "losing his mind" may be allayed; he can be told factually and honestly that there is no specific medical therapy for aphasia, and can be impressed with the necessity for retraining.

We have recently had an interesting experience in the management of hemiplegia in our own department.[6] Birch attacked the problem by attempting to modify the "block" rather than accept the theory of subtraction. He chose 14 aphasic patients who had been under therapy for six months or longer and who had a vocabulary of less than 5 words. By giving them a shocking dose of sound,

he found that in a matter of seconds their vocabulary increased from 12 to 15 words and by continuing the shock over longer periods of time, gains could be increased and maintained. More than 80 per cent of the initial group were trained to the point of adequate vocabulary for daily use. While the series is far too small for any conclusion, it certainly presents an interesting approach to a most difficult problem.

Hemiplegia presents one of the most challenging problems in medicine today, both in total numbers and therapeutic complexities. With a dynamic approach to the problem of the hemiplegic, using rehabilitation techniques that have been developed to meet the total needs of the individual, much can be offered to these severely disabled patients, and many can be trained so that they achieve lives of self-sufficiency and usefulness.

A great neurologist of our time, Spiller, gave one of the therapeutic keys to modern rehabilitation when he said, "Action absorbs anxiety." Directed action does more than absorb anxiety. It can provide the tools for learning that can take a surprising percentage of even the elderly neurologically handicapped back to lives of comfort and self-care, and many back to gainful occupations. If one word could be used to designate the therapeutic goals in such a program, it would be the attainment of dignity.

)L.
4
956

REFERENCES

1. Treatment of Chronic Neurological Patients in the Veterans Administration Hospital, Minneapolis, Minnesota. Unpublished report.
2. Statement "Neurological and Sensory Disorders" Prepared for the Hearings of the House, Committee on Interstate and Foreign Commerce, Oct. 7, 1953, Washington, D. C., by the National Committee for Research Into Neurological Disorders.
3. Dacso, M. M., Novey, J., Kristeller, E. L., and Rusk, H. A.: Rehabilitation Monograph VII: A Survey of Ninety-Five Custodial Patients in a Municipal Hospital, New York, 1954, Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center.
4. Unpublished data from the Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center.
5. Rusk, H. A., et al.: Hemiplegia and Rehabilitation, Seminar, January-February, 1952.
6. Unpublished data of Herbert G. Birch, Ph.D., Research Associate, Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, 1955.

PRINCIPLES AND TECHNIQUES OF MEDICAL REHABILITATION

JEROME S. TOBIS, M.D.*

NEW YORK, N. Y.

From the Department of Physical Medicine and Rehabilitation, New York Medical College

(Received for publication Dec. 10, 1955.)

VOL
4
195

PHYSICAL medicine and rehabilitation is a medical specialty which concerns itself with the care of the chronically ill and severely disabled. This group of patients is steadily increasing in number. It has been estimated that there are approximately 28,000,000 people in the United States with chronic disease.[1] The estimated number of persons with long-term disabling chronic disease or impairment was 5,300,000 in 1950.[2] Of this number, 2,100,000 (39 per cent) are estimated to be in the older age group, 65 years and over; about 1,800,000 (34 per cent) in the middle span are 45 to 64 years of age; and 1,400,000 (27 per cent) are under 45 years of age.

Many factors have contributed to the marked increase in the number of chronically ill. Among the major factors which have lengthened the life span are: (1) advances in the techniques of medical care, (2) improved public health facilities, and (3) general improvement of the standard of living.

These factors are indigenous to our society, with a resultant permanent rise in the older population; and in the years ahead we may anticipate an increase in the number of chronically ill. Out of the recognition of these problems the field of physical medicine and rehabilitation has grown and matured. Many papers and books[3] have appeared in recent years to demonstrate the medical, economic, and social value of rehabilitation techniques in the care of the chronically ill. The objective of this paper is to present the physiologic principles for the techniques employed in the rehabilitation care of patients.

The field of physical medicine and rehabilitation directs its activities to the care of patients with major disabilities which include a spectrum of disease ranging from neuromuscular and musculoskeletal disorders to cardiac and cerebrovascular dysfunctions. Depending upon the severity of the disability and the facilities available, patients may be treated either in a home, a physician's office, or a hospital.

Presented on Oct. 27, 1955, at a Two-Day Conference held at the New York Medical College and Bird S. Coler Hospital, on "The Practice of Medical Rehabilitation-Home, Office and Hospital Procedures."

*Professor and Director, Department of Physical Medicine and Rehabilitation, New York Medical College, New York, N. Y.

OL.
4
956

PRINCIPLES OF CARE

The principles of care for the home, office, or hospital are essentially the same, but the techniques vary in these three settings. This paper seeks to outline what can be done in each area. Chronic disease is usually regarded as an institutional problem. However, the predominant number of patients suffering from chronic disease are managed, if at all, either at home or in the office. Rehabilitation, therefore, is the responsibility of every physician.

The philosophy of rehabilitation signifies total care. It looks upon disability, as medicine does generally, as more than the specific illness. For example, the diabetic amputee suffers not only from the degenerative processes caused by the metabolic disorder, but by the impact of the social problem created in his family as a consequence of the amputation. Chronic disease has a social character as well as a biologic one and the patient requires, in addition to the traditional specific clinical care, the services of additional medical and nonmedical staffs who function as a team. This team directs its efforts toward attaining maximum function for the patient in the physical, psychologic, vocational, and social spheres. Whereas all of these factors exist in the acutely ill patient, their impact is not as strongly felt because the disease is self-limited and recovery from the illness permits a return to previous levels of function. Treatment-planning in the acutely ill is therefore restricted to the medical and nursing aspects of care.

Treatment-planning in the chronically ill, on the other hand, must attempt to provide not only the medical and nursing needs but the social, psychologic, and vocational ones as well. Medical programming for the patient with chronic disease must be long range in character. These patients need one physician who can guide the family and supervise the over-all care. The family doctor may call upon the advice and skills of many specialists whether it be the physiatrist (specialist in physical medicine), orthopedist, or neurologist, but only the physician who can provide on-going care and supervision over a period of months or years is in a position to manage the care effectively. Too often patients obtain excellent care for a limited period of time only to regress or to be left in a void because of lack of continuing guidance.

PHYSIOLOGIC PRINCIPLES

There are three major areas of physiologic activity in rehabilitation, namely: motor activity, cardiovascular function, and the learning process.

1. *Motor Activity.*—Any consideration of motor activity must take into account the musculoskeletal structures and the nervous apparatus which activates them.

Muscle: Since it is well established that one of the factors of motor power is muscle bulk, we seek to develop motor power by hypertrophy of muscle fibers. This is attained through active or resistive exercises in which the patient performs work. This activity leads to an increase of motor power. The essence of such exercise is the active participation of the patient, because only through the expenditure of energy will muscles increase in bulk. Passive exercises, on the other hand, such as massage or stretching, will not improve motor power no matter how long the procedure is performed.

Bone: It is axiomatic that bone formation and resorption are maintained in a state of dynamic equilibrium and are influenced by motor activity. For example, it has been clearly established that prolonged immobilization of more than ten weeks leads to osteoporosis and concomitant deposition of calcium calculi in the kidneys and muscles.[4] On the other hand, weight-bearing aids in the formation of the osteoid protein and deposition of calcium in the bones. Thus, the patient will show the end results of these dynamics depending upon the care and activity provided. For example, in patients with arthritis, paraplegia, and poliomyelitis, osteoporosis is in part due to immobilization and disuse. It is, therefore, essential that the doctor who confines a patient to bed recognize it as a medical prescription which has indications and contraindications. Because of the deleterious metabolic and psychologic consequences of prolonged bed rest, it should be discontinued at the earliest feasible moment. Convenience to nurse or family is insufficient basis for its continuation.

Nerve: The first principle of muscle function requires that the muscle be innervated. The judicious application of principles of neurophysiology to clinical problems facilitates treatment-planning. Thus, in damage to the anterior horn cell as in poliomyelitis, the cell is either recovered or completely lost within weeks. A portion of the muscle may thus be completely denervated. From our experience, with adequate treatment, one year should be sufficient to give maximum power of the remaining innervated muscle fibers. Yet, patients or their families continue to seek additional therapy for the patient who has had adequate treatment, years after the initial attack, in the hope of regaining innervation of new motor power.

2. *Cardiovascular Function.*—The second important area of physiologic activity is cardiovascular function. Exercise tolerance is dependent upon cardiovascular tolerance. The participation in active exercise leads to an increased tolerance of the cardiovascular system, with an increased stroke volume, a relative decrease in pulse rate, and greater vasomotor stability. On the other hand, immobilization and bed rest may bring about a definite deterioration in the mechanisms essential for adequate circulation in the erect position. Thus, getting a patient up out of bed will influence favorably the catabolic effects on bone and muscle and will also improve cardiovascular function.

3. *Learning Process.*—The third area of physiologic activity in rehabilitation is the learning process. This is a basic neurophysiologic activity of man which involves both sensory and motor apparatus. Rehabilitation involves a learning or relearning process. The objective is the learning of skills by the patient who must utilize the potential of the structure and functions which remain. The brain determines all motor activity and this motor activity, in turn, is dependent upon the capacity of this brain to receive and organize sensory stimuli.

Motor function is, from this approach, the end response to the perception and organization of exteroceptive and interoceptive stimuli. It is for this reason that we disagree with the use of the phrase "muscle re-education." Muscles are never re-educated. Human beings with a cortex are.

VOL 4 195

Based on these physiologic considerations, two principles may be stated. First, rehabilitation requires the active participation of the patient. If he has pneumonia, the success of treatment is largely determined by the effectiveness of the antibiotic prescribed by the physician and by the nursing care provided. In rehabilitation, he must participate actively in order to gain new function.

Second is symptomatic treatment. Although an understanding of the pathologic physiology of the disease is essential to evaluate prognosis and contraindications for treatment, rehabilitation therapy is not directed to the disease process itself but to the symptomatology.

In applying these principles to the care of the chronically ill, the field of physical medicine and rehabilitation has developed skills and techniques which are not new, but, rather, their application has become more sharply defined. The physician should be familiar with these skills and techniques. He should understand the indications and contraindications for their use. Many may be carried out by the physician himself, others may be taught to the patient's family to perform. Still others are best done by those specially trained. Just as the physician does not personally do all of the laboratory procedures that he prescribes, so too should he call upon the skills of others for special rehabilitation techniques that he is not prepared to perform.

OL.
4
956

MODALITIES

Physical medicine techniques are prescribed for three major objectives: (1) relief of pain, (2) increase in range of motion, and (3) increase of motor power. The modalities used consist of heat, massage, exercise, electrotherapy, hydrotherapy, ultraviolet radiation, and cold therapy.

Heat is a valuable agent in providing the relief of pain in musculoskeletal disorders such as rheumatic diseases. Heat may be provided by conduction, convection, or radiation. It may be given to superficial structures by a hot-water bag, paraffin bath, or an infrared lamp, or to deep structures by a diathermy, microwave, or ultrasound machine. The end result of the judicious use of such agents will be (1) increased blood flow to the part, (2) an analgesic or hypalgesic effect, and (3) the relief of muscle spasm. Often, heat application may be supplemented by the use of massage. The use of heat is contraindicated in the presence of arterial vascular disease when the rise in tissue metabolism due to the heat cannot be met by increased blood flow. It is contraindicated in the presence of malignancy. In the presence of an acute inflammation involving a nonexpansible area such as bursitis, the use of heat may exacerbate the pain. In these conditions, cold in the form of ice or ethylchloride spray may be used as an analgesic.

Another technique which may be employed for the relief of pain is the passage of a drug into the superficial tissues with the use of low-voltage electrical current (iontophoresis). Drugs such as histamine hydrochloride or Novocain may be introduced effectively by this means and result in the relief of pain locally. Such drugs may have other pharmacologic effects. Thus, histamine is a vasodilator which may be introduced in arterial peripheral vascular disease without a rise of tissue metabolism.

Low-voltage currents are also employed as a diagnostic and therapeutic tool in the evaluation of peripheral neuropathies. The changes in muscle response to different types of current, such as faradic and galvanic, help in establishing diagnosis as well as prognosis. As a therapeutic tool, electrical stimulation of a functionally or anatomically denervated muscle is of value in reducing the rate of atrophy until reinnervation may occur.

A much overused but nonetheless valuable modality is hydrotherapy. It is an effective agent for providing heat. In its most popularized form as whirlpool, it has a cleansing action and some mild sedative effect. In diseases of the peripheral nervous system such as poliomyelitis, water reduces the effect of gravity and thus permits a weakened muscle to contract and produce movement.

Another useful physical agent is ultraviolet light, which may be valuable in the healing of ulcers because of its bacteriostatic effect and its capacity to stimulate epithelization. It also has a useful role in dermatologic conditions.

Exercise is a major physical modality employed in rehabilitation because it enables the patient to gain greater function. Range of motion of a joint may be increased by the use of passive exercises or stretching. However, only active exercises will provide increase of motor power, and such exercises may be graduated from assistive, to active, to resistive. Such exercises may also be performed by the use of occupational therapy procedures, utilizing specific functional goals to obtain an increase in motor power or in range of motion.

The use of braces, prostheses, and self-help devices must be considered as medical prescriptions. Their role is to provide the patient with substitutions for a lost structure such as an artificial limb, or as an assistive device for obtaining greater function. Bracing may be utilized for (1) stabilization of a joint, (2) prevention of deformity, and (3) correction of deformity. It is important to re-emphasize that this area of prosthetics has provided many new advances to help the severely disabled. However, no device will be effective without the participation of the patient. He must still be capable of using them.

The three major complications of chronic illness are (1) contractures, (2) decubiti, and (3) metabolic deterioration such as osteoporosis and muscle atrophy. Physical medicine and rehabilitation can prevent many of these complications by the rational use of appropriate therapeutic tools. When these measures fail to cope with an existing complication, the services of acute care must be called upon, such as plastic surgery for decubiti, orthopedic surgery for contractures, or neurosurgery for intractable pain.

This review of techniques of rehabilitation has thus far concerned itself with the physical disability of the patient. The psychologic, social, and economic aspects of the patient's disease must also be evaluated and treated. Interference in the psychologic functioning of the patient in the areas of intellect and language are frequently seen in hemiplegia and cerebral palsy. Here the physician should call upon the psychologist and speech therapist. Their skills include not only objective testing but counseling and training. This will help the physician to bring the patient to the maximum function of which he is capable.

Finally, with the assistance of the vocational counselor and social worker the patient's previous vocational capacities, work, education, and family situation may be evaluated and the possibilities for returning him to a socially productive life explored.

In summation, the use of physical, psychologic, and social techniques will vary from one patient to the next, depending upon his needs. Many of them may be employed by the physician or by the family under the supervision of the physician. Some will require the participation of community agencies such as for vocational training. All physicians should provide, with the assistance of, and in consultation with, others when necessary, the total care that is the sine qua non of good medical care of the chronically ill. Rehabilitation means good total medical care.

Rehabilitation does not require luxurious facilities. For the vast majority of the chronically ill, rehabilitation can be effectively provided at home or in a physician's office. For the minority who need more extensive facilities, a hospital is required.

OL.
4
956

REFERENCES

1. Woolsey, T. D.: Estimates of Disabling Illness Prevalence in the U. S., Public Health Monograph No. 4, Public Health Service Publication No. 181, Washington, D. C., 1952, Government Printing Office, 16 pp.
2. Perrott, G. St. J.: Care of the Long Term Patient: Source Book on Size and Characteristics of the Problem, Reprint of Public Health Service, Publication No. 344, Government Printing Office, Washington, D. C., 1954.
3. Buchanan, J. J.: New Hope for the Severely Handicapped and the Chronically Ill. In Total Evaluation of the Client; Proceedings of the Fifth Annual Workshop of Guidance, Training, and Placement Supervisors, Washington, D. C., Office of Vocational Rehabilitation Service Series No. 188, 1952.
   Covalt, N. K.: Physical Medicine and Rehabilitation Study; One Year Report in Particular Relation to Chronically Ill, J.A.M.A. **144**:1249, 1950.
   Dacso, M. M., and Grynbaum, B. B.: Physical Medicine and Rehabilitation Service at Goldwater Memorial Hospital, Chronic Illness News Letter **2**:1951.
   Rusk, H. A., and Taylor, E. J.: New Hope for the Handicapped, New York, 1946, Harper & Brothers.
4. Dietrick, J., Whedon, G., and Shorr, E.: Effects of Immobilization Upon Various Metabolic and Physiologic Functions of Normal Man, Am. J. Med. **4**:3, 1948.
   Keys, A.: Deconditioning and Reconditioning in Convalescence, S. Clin. North America **25**:442, 1945.

BASIC MEDICAL PRINCIPLES IN THE TREATMENT OF THE CHRONICALLY ILL PATIENT

KARL HARPUDER, M.D.

NEW YORK, N. Y.

From the Department of Physical Medicine and Rehabilitation, New York Medical College

(Received for publication Dec. 10, 1955.)

VOL.
4
195

BEFORE discussing problems of treatment, I wish to emphasize three self-evident principles: (1) The goal of treatment is recovery of maximal physical, intellectual, and emotional function of the chronically ill patient within the limits of his disability. (2) Medical care has to be total from its onset. There are no separate phases of care for the chronically ill. One cannot wait with rehabilitation until the cardiac is completely compensated and the arthritic inactive. One cannot shelve cardiac care in the rehabilitation of a hemiplegic with arteriosclerotic heart disease. (3) Sound relationship between possible gain and possible hazard of a treatment is especially necessary in the chronically ill. This is particularly true of rehabilitative measures. One can take a calculated risk with a toxic drug in acute leukemia. One cannot take a chance that a hemiplegic may fall and fracture a hip by forcing him to walk beyond capability.

With these principles in mind, some of the problems in the treatment of chronic illness can be reasonably delineated. To avoid useless generalities the discussion will concern the most common categories of chronic diseases, namely: cardiovascular, neoplastic, neurologic diseases, and arthritis. It will deal with the bedridden and with the ambulating patient.

Some problems are present in most of the chronically ill. They will be taken up first.

1. *Metabolism and Nutrition.*—In the bedridden patient these factors are severely disturbed. Nitrogen balance, calcium, phosphate, and sulfate balance are negative. There is loss of body substance, muscle atrophy, and osteoporosis. It is extremely difficult to correct these metabolic deviations with excess proteins in the diet or parenterally. A poor appetite often does not even permit a normal food intake and cannot be improved by the administration of vitamins, testosterone, or insulin. Osteoporosis, especially common in the female postmenopausal patient, is not influenced by calcium feeding and doubtfully over long periods of time by estrogens and androgens or a combination of both. Salt-poor diets, often used indiscriminately in hypertensives and for better reasons in

Presented on Oct. 27 at a Two-Day Conference held at the New York Medical College and Bird S. Coler Hospital, on "The Practice of Medical Rehabilitation-Home, Office, and Hospital Procedures."

cardiac failure, further undermine the appetite and increase the metabolic difficulties of the chronically ill, bedfast patient.

The metabolic deterioration of bed rest, disuse atrophy of muscles, and osteoporosis are most effectively minimized by activation of the patient. This may mean active assistive and resistive exercises and some weight-bearing several times daily with the aid of family members or technical personnel. This must be kept within the tolerance of the severely ill bedfast patient. In rare instances, exercise and weight-bearing may have to be carried out in an oscillating bed. However, more often than not, the bedridden patient can be made to stand and/or walk, if needed with help, several times a day. The use of a commode is much preferred to the bedpan because it involves more patient participation and less effort and strain. In cases of severe osteoporosis and partial vertebral collapse, it may be necessary to support such patients by the use of spinal braces and bedboards.

OL.
4
956

With such a program of progressive activation it is frequently possible to obtain a fairly satisfactory metabolic balance with a normal protein-rich diet of 2,500 calories if well-prepared and varied enough to arouse the patient's interest. A salt-poor diet may on one or two days a week be amended by a small measured amount of salt unless contraindicated. The appetite may also be better stimulated by a little wine or brandy than by yeast-tasting vitamin B tablets.

2. *Activation of the bedridden patient within the limits of his ability.*—This is also of aid in avoiding other complications of extended bed rest. Especially in cardiacs, neoplastic diseases, and in debilitated patients, the most common and dangerous complication is phlebothrombosis. This may develop without or with minimal evidence on physical examination and may suddenly terminate life by a massive pulmonary embolus. It may be complicated by multiple small embolizations resulting in pulmonary fibrosis. The site of the thrombosis is often the deep veins of the lower extremity including those of the foot, and sometimes the pelvic veins. Anticoagulant therapy or vein ligation are the two methods of active treatment once the thrombosis is established and recognized. Both these methods of treatment have considerable disadvantages in the chronically ill. It is pertinent to bear in mind that phlebothrombosis rarely develops in activated patients. Even exercises in bed several times daily have a prophylactic value, although they are not a complete protection. Active exercises should also be started during anticoagulant therapy a few days after a satisfactory antithrombin level is reached. While exercise is useful in preventing phlebothrombosis, excessive exercises under the direction of a too-vigorous and enthusiastic therapist may cause an effort-thrombophlebitis. A word of caution by the supervising physician is therefore desirable. It is hardly necessary to mention that massage is strictly contraindicated in the presence of venous thrombosis. It is also obvious that sitting in a chair or on the edge of the bed for hours without moving the legs is worse than bed rest.

3. *Flexion Contractures in Knees and Hips and Shortening of the Achilles Tendon.*—These are other complications of continued bed rest which can be avoided by proper exercise. Flexion contractures of the knees and more rarely

of the hips result when a painful lesion on the foot or toes produces a withdrawal reflex or when a painfully inflamed knee can be relieved by flexion and the consequent diminished tension. These contractures are therefore most frequently seen in patients with gangrene or ulcers on the foot or with active arthritis of the knees. Irreversible deformities develop with great rapidity and are not even suitable for surgical correction. They add immeasurably to the disability of the patient. Shortening of the Achilles tendon occurs readily in debilitated bedridden patients when the bedcovers depress the foot or in neurologic diseases with a spastic or flaccid paralysis of the foot.

It is therefore mandatory to apply stretching exercises in all bedfast chronically ill patients with a tendency to contractures. In many cases these can be carried out by the patient or by family members. If the first evidence of contracture appears, skilled help for stretching exercises is required. If the patient cannot cooperate, splinting devices may be necessary. The ankle should be supported on footboards, sandbags, or with a splint. Stretching exercises should be through the complete range of motion if possible. They should never be traumatic or one loses the patient's cooperation. Organic damage may also increase the final contracture. This is also true of traumatic stretching under anesthesia. If stretching by mechanical means is necessary, traction or a turnbuckle device may be applied. In a rare case tenotomy and capsulotomy is required in the absence of severe vascular impairment or active arthritis.

It is best, however, to prevent contractures by early adequate and persistent exercises and mobilization of the patient.

4. *Decubitus Ulcers.*—A scourge of the bedfast patient and his physician is the appearance of decubitus ulcers. These are most frequent in neurologic patients with sensory loss and loss of sphincteric control, but are also common in debilitated patients and in those with poor skin circulation. Decubiti occur over all pressure areas, shoulder blades and elbows rarely, sacrum and trochanteric areas most often, and heels frequently. If the patient spends time in the prone position, they are seen over knees and anterior spines. They may develop almost overnight or may take weeks. Decubiti may vary from bluish discoloration, to hemorrhagic or gangrenous blisters, to superficial gangrene, or to deep necrosis even involving bone. Gangrene is followed by sloughing, infection, and ulceration.

Prevention of bedsores is a nursing responsibility and is in most instances possible by meticulous nursing care. Maintenance of good nutrition is of great importance.

Frequent turning of the patient and keeping the back clean and dry do a great deal to avoid bedsores. Heel pressure may be minimized by having a firm flat pillow extend from mid-thigh to above the ankle. This will not favor flexion in the knee. In helpless patients and with limited nursing facilities, an air inflation mattress with alternately inflated and deflated air compartments may be advisable. Paraplegics may require a Stryker frame.

The best protection of the patient is to activate him. If he is willing and able to turn himself over, the nursing problem is so much easier. If he can spend time in a chair sitting on a ring or a foam rubber pillow, the danger of

VOL. 4 1956

decubitus is decreased and still more so if he can stand up and walk even though support may be necessary.

Superficial decubitus can be managed conservatively, although often with much difficulty. Deep necrosis needs surgical débridement and plastic surgery. Such lesions can sometimes be débrided chemically with Varidase or Tryptar. Antibiotic ointments are generally useless and possibly detrimental. Irrigations with saline or tyrothricin may be helpful. A clean wound may heal faster under ultraviolet radiation. If circulation in the ulcer area is poor, histamine by ion-transfer around the ulcer is a means of increasing the local blood flow. A large infected decubitus requires systemic antibiotic therapy which may present a difficult problem in the presence of multiple and often resistant infecting organisms. Uncontrolled decubitus is a potential source of blood stream infection, amyloid disease, and increased spasticity.

A great danger for the bedfast chronically ill patient is intellectual and *emotional deterioration.* Emotional complications and intellectual damage are common in the aged with chronic disease. Confinement to bed greatly magnifies the frequency and severity of these disturbances or their manifestations. Psychologic and psychiatric interviews in some instances may be of less value than proper planning of diversional and occupational activities and activities of daily living.

The problems common to the various types of chronic illness are at least partly due to the inactivation of bed rest. They can in most instances be avoided or minimized by activating exercises in bed, periods of chair activity, ambulation, diversional and occupational activities.

However, it must be emphasized that activation of the patient with chronic illness cannot be carried out routinely and dogmatically. There is needed a thorough knowledge of the disease process and its influence upon the physical abilities and the emotional and mental reactions of the patient. The program has to be carefully prescribed, supervised, and modified by the physician. The patient, the family, and technical personnel must be guided with consideration, patience, and persistence. Otherwise, the rehabilitation effort will come to nothing or a too vigorous effort will end up with a very ill, even more disabled patient. The program does not in most cases require permanent hospital care; it can often be carried out in the patient's home and by family members if necessary with the aid of a visiting nurse and/or a physical therapist.

Special problems arise in the various types of chronic diseases.

1. With the extension of the life span and the improvement of the diagnosis and treatment of acute coronary artery disease, chronic myocardial disease acquires more and more importance. Even when the patient is in failure, passive and brief assistive active exercises are permissible and probably valuable in minimizing phlebothrombosis and excessive physical and moral deterioration. The strain of such careful exercises is minimal compared with that of an enema and a session on a bedpan. With improving compensation, exercises should be increased within the limits of cardiac reserve. Walking exercises are gradually added with extended distances and tempo. If possible, stair walking and occupational activities follow. To accomplish the most and to avoid trouble, one

must thoroughly understand the disease and the circulatory effects of exercise. Changes in pulse rate and respiration, variations in blood pressure, the appearance of cardiac irregularities, a little cyanosis, chest pain, and sometimes the electrocardiogram, indicate the limitations of the patient's physical ability. The publicity given in recent years to coronary artery disease; the previous medical dogma of complete bed rest for six to eight weeks for the patient with a myocardial infarct, to be followed by severe limitation of physical activities for an indefinite period of time—these factors have created a serious psychologic difficulty in many instances. Many months or even years after the "heart attack" and without evidence of failure, the patient is afraid of the slightest physical effort and unable to resume work. This is not a problem for the psychiatrist. It is the practitioner who treats the heart, knows the patient, and has his confidence, who must use his influence and knowledge from the beginning, in order to stave off emotional crippling of the patient.

Serious disability sometimes results in patients with myocardial infarcts from development of the so-called shoulder-hand syndrome and/or Dupuytren's contracture. The etiology is not clear but these syndromes are preventable by early exercises for upper extremities, and at their beginnings perhaps reversible by stellate ganglion block and proper exercises.

2. Another disease with special problems is obliterative arteriosclerosis with thrombosis which develops frequently in the lower extremities. It causes intermittent claudication, ischemic neuropathies, ulcers, and gangrene with pain at rest. In most instances the process is chronically progressive, sometimes rapidly so. Varying degrees of disability result, from long periods of bed rest and major amputations at worst, to severely or only slightly diminished walking ability in the milder or mildest cases. In a few instances with segmental occlusion, active treatment consists of surgical removal of large thrombi or resection and blood vessel grafting. Conservative measures are medical, physical, or surgical production of vasodilatation, and anticoagulant therapy. In the presence of severe trophic changes, no form of therapy offers much promise. It is the early case which benefits from preventive measures and active treatment. While at bed rest the patient needs exercises to avoid flexion contractures of the knee, hip, and ankle. He needs general exercises to avoid muscle wasting and metabolic deterioration. Except in cases of gangrene, larger ulceration or infection, walking should be encouraged, however avoiding severe claudication pain. Exact foot hygiene, careful protection against even minimal trauma, and warning against any form of direct heat application are a must. In an amputee, prevention of any injury to the remaining foot and prophylactic vasodilator therapy are indicated even in the absence of a clinically impaired circulation.

The patient with chronic arterial disease without gangrene or infected ulcer and the vascular amputee should return to work. Distance walking, stair climbing, exposure to cold, and traumatic hazards to the foot must be avoided. These patients frequently need much encouragement especially if they were terrified by the diagnosis of "hardening of the arteries" or by their own knowledge of gangrene and amputation in relatives.

VOL 4 195

OL.
4
956

3. Progress in surgery, chemotherapy, and antibiotic therapy have thoroughly changed the outlook in neoplastic diseases. Although cures may not be possible in many instances, life span has been considerably extended even in the presence of metastatic spread. Unless neoplasia is cured or takes a rapid course as is the case in acute leukemia, it should be considered a chronic disease. The fact that a fatal outcome is expected in a few months or years must not deter us from treating the chronically ill patient with a view to his greatest comfort. While in bed after surgery or for other reasons, the patient requires nursing care, nutritional management, and exercises to avoid bed sores, phlebothrombosis, and metabolic deterioration. Ambulation, training in self-care, and diversional and occupational activities are possible even in the presence of bone metastases and osteoporosis. Metastatic and osteoporotic back pain may be relieved by orthopedic corsets or braces which offer also some degree of protection against pathologic fracture and collapse. A woman with bone metastases after a mastectomy may live for several years and carry out household duties if encouraged and helped to do so. A patient with a glioma of the spinal cord, temporarily stationary after x-ray therapy, should be managed like a paraplegic of any other stationary etiology. An emaciated tumor patient full of pain, increased by every movement of the body, should be given relief by sedation and not be made to suffer by ambulation.

4. Rheumatoid arthritis is the prototype of a chronic disease, with a protracted course of progressive joint inflammation and destruction over many years, finally leaving the patient with severe permanent disability. Although periods of complete bed rest may be necessary during phases of great joint inflammation, this can be avoided or limited to a few weeks in most cases. During bed rest, the danger of crippling flexion contracture of knees and hips, muscle atrophy, and osteoporosis is especially great. The same precautions should be taken as outlined above. Most arthritics may be ambulatory or semiambulatory, some chair-bound. It is still impossible to cure arthritis or permanently to arrest its progress. Steroid hormones and butazolidin act as anti-inflammatory agents during the period of application. Gold therapy is of doubtful value. All these drugs have undesirable or dangerous side effects which cannot always be avoided. Salicylates are moderately good pain relievers. Treatment of arthritis then consists of improving nutrition, and of checking inflammation and pain at least temporarily with the above drugs. Physical therapy and rehabilitation must be instituted as soon as joint inflammation has been brought under tolerable control. It is essential to keep the patient walking and using his hands and shoulders. Active and passive range of motion exercises to all joints several times daily should be given carefully enough to avoid trauma. Resistive exercises on noninvolved joints and muscle setting on involved painful joints help to maintain muscle power. Heat applications relieve pain, relax muscles, and sometimes reduce chronic inflammations. Splints may be required to avoid contractures of knees and elbows. Finger deformities, however, develop in spite of the best care. Spinal braces, knee braces, or walking braces may have to be given for the sake of protection and correction of postural anomalies.

Confronted with a chronic progressive and destructive disease, the patient needs moral support. Maintenance of occupation or light housework is very important. Diversional activities are a mediocre substitute for more purposeful and productive activities. The patient should be treated in the home with the aid of family, visiting nurse, or therapist, or be handled on an ambulatory basis. Hospitalization should be a rare exception.

5. The most common neurologic problem in general practice is hemiplegia on the basis of a cerebral vascular accident. There is no medical therapy of proved value during the acute stage or during the rehabilitation phase. Stellate ganglion blocks are of doubtful effect. The recently recommended use of cortisone in large doses carries the possible dangers of thrombosis and edema and should not be applied except in a hospital. During the acute stage, nursing and general medical care are most important. Passive range of motion exercises and, as soon as possible, active exercises of noninvolved extremities probably help to avoid venous thrombosis. As soon as the patient comes out of coma and central nervous system shock, he should be helped to sit up for fifteen minutes twice daily with sufficient support. His legs should be moved while in the dependent position. With the first return of active motion, even if only in the hip movers, attempts at standing and walking begin. If the paretic lower extremity is in extensor spasticity, walking will be possible without active motion in knee movers. There may be need for a drop foot brace. If spasticity is moderate and weakness marked, stabilization of the knee with splint or brace may be required. The training process for walking is long and laborious. The upper extremity, spastic and paretic, rarely recovers enough skill to be useful. There is no medication to relieve excessive spasticity, and no means of increasing muscle power except by spontaneous neurologic recovery and by exercise. The shoulder-hand syndrome in the hemiplegic rarely responds to therapy including stellate ganglion blocks. Another difficulty is the development of a downward dislocation of the paralytic shoulder which may require a supportive sling. Some of the self-help devices are useful in training the patient for daily living activities.

Complications frequently interfere with the progress of rehabilitation. These patients often have multiple cerebral lesions and are mentally deteriorated. Lack of motivation does not correctly state the problem. Arteriosclerotic heart disease, peripheral arteriosclerosis, emphysema, and diabetes are often present. Therefore, the rehabilitation of the patient with a cerebral vascular accident needs the careful supervision and guidance of a physician who understands the patient, his disease, and the physiologic effects of rehabilitation techniques.

VOL 4 195

UNTREATED SYPHILIS IN THE MALE NEGRO

X. Twenty Years of Clinical Observation of Untreated Syphilitic and Presumably Nonsyphilitic Groups

Sidney Olansky, M.D.,* Stanley H. Schuman, M.D.,** Jesse J. Peters, M.D.,*** C. A. Smith, M.D.,**** and Dorothy S. Rambo, R.N.*****

Washington, D. C.

From the Venereal Disease Program, Division of Special Health Services, United States Public Health Service, Washington, D. C.†

(Received for publication Nov. 5, 1955.)

OL.
4
956

THIS report summarizes the clinical status of the members of the Tuskegee study who were living and examined in the twentieth year of observation. Particular attention will be given to evidence of late syphilis in the group and to abnormalities of the cardiovascular system in the syphilitic and nonsyphilitic groups.

Eventually, a clinicopathologic correlation between syphilitic and nonsyphilitic groups will be required, but a valid final analysis will not be possible until the majority of the patients will have lived out the total life experience.

Thus far other papers of the series have discussed the adverse effect of syphilis on life expectancy,[1,2] have shown in the group coming to autopsy the pathologic changes resulting from syphilis,[3] and have, throughout the series of examinations, shown a greater amount of physiologic change, not necessarily specifically syphilitic, among the syphilitic patients.[4] The shortening of life expectancy observed in man, which can in part be explained on the basis of specific anatomic changes,[1,2] has a counterpart in the white mouse, in which animal it has been shown by Rosahn[5] that a syphilitic group has a significantly lessened life expectancy even though it has not been possible to demonstrate specific microscopic lesions of syphilis. The question has been raised as to the possible mechanisms of this adverse effect, but answers are not as yet available. Within the human group a similar shortening of life span is noted which, at least in part, can be correlated with specific, more or less lethal anatomic changes. The specific factors concerned with this shortening in syphilitic patients remain to be

---

This article is one of a series on untreated syphilis in the male Negro which the Venereal Disease Program, Division of Special Health Services, plans to assemble into a monograph. Single copies of the monograph will be made available upon request to the Venereal Disease Program, Division of Special Health Services, United States Public Health Service, Washington 25, D. C.

*Formerly Director, Venereal Disease Research Laboratory, Chamblee, Ga. Present address: Duke University, Department of Medicine-Dermatology, Durham, N. C.

**Formerly, Senior Assistant Surgeon, United States Public Health Service, Venereal Disease Research Laboratory, Chamblee, Ga. Now in private practice.

***Chief, Radiology Service, Veterans Administration Hospital, Tuskegee, Ala.

****Chief, Venereal Disease Program.

*****Statistician, Venereal Disease Research Laboratory.

†With statistical assistance from the Office of Statistics, Venereal Disease Program.

determined. In the present report of findings observed at the twenty-year mark, attention is given not only to the cardiovascular and nervous systems but to some general attributes of health in an attempt to elucidate the problem.

DIAGNOSIS OF SYPHILITIC HEART DISEASE

As interest in detection of early and slight cardiovascular complications in these men grew keener over the years among the various medical examiners, increasing use of the x-ray and fluoroscope was made. In 1932, chest films in the posterior-anterior view of all the men were taken at the John Andrew Memorial Hospital in Tuskegee, and these films proved a valuable base line for comparison with later ones. In subsequent physical examinations, all those examined received x-rays of the chest in multiple views (posterior-anterior, left anterior oblique, and right anterior oblique) with barium swallow. From these films it was possible to measure heart sizes (in the manner of Bordet-Vaquez and Fray), the aortic diameter at the knob, the width of the aortic arch, and to calculate the various cardiothoracic ratios. Diebert in his report in 1946[4] called attention to certain striking differences in the aortic-cardiac measurements of syphilitic compared to nonsyphilitic patients. Those x-ray measurements have been made at each examination so that data are accumulating which should reveal long-range trends in the changing size and contour of the heart and aorta as seen radiologically. During the first examination fluoroscopy was done on only a few patients suspected of aneurysm. Later fluoroscopy became routine for nonsyphilitic individuals as well as syphilitic ones. The pathologist in this study (Dr. J. J. Peters) has been studying the correlation of ante-mortem x-ray measurements with post-mortem data for future publication. In addition to chest films, x-ray studies have been made of long bones and the skull wherever necessary to confirm diagnoses of syphilitic osteitis.

X-RAY DIAGNOSIS OF SYPHILITIC HEART DISEASE

During the period of this study many radiologic criteria have been proposed for earlier or more precise diagnosis of syphilitic heart diseases. The lack of value of any of the proposed criteria based upon aortic mensuration has been adequately documented by Kemp and Cochems.[6] In this series, the unreliability of any of the criteria proposed during the twenty-year period has been shown in the group coming to autopsy. Among individuals with a history of syphilis, the diagnosis of uncomplicated syphilitic aortitis made during life was confirmed in only half of the patients, thus pointing up the inadequacy of diagnostic criteria with which it still is necessary to work. While the diagnosis of syphilitic aneurysm and of syphilitic aortic insufficiency can be made ante mortem with a relatively high degree of accuracy, it is as yet not possible to diagnose satisfactorily uncomplicated aortitis. No informative discussion of aortitis based on this study group can be prepared until the larger part of the group has come to autopsy.

X-RAY ABNORMALITIES

No attempt was made to classify abnormalities as to syphilitic etiology except for those patients known to have saccular aneurysm. Table I shows

that there is a higher degree of abnormality in the syphilitic group than in the control. Such results suggest that men with untreated syphilis may be predisposed to changes in their cardiovascular systems which readily will be recognized as abnormal by the radiologist, although he cannot categorically ascribe these changes, in part or altogether, to a syphilitic process. In other words, the question arises as to whether the majority of changes in the aorta as the result of syphilitic involvement are sufficiently distinctive to permit of accurate diagnosis during life by the techniques now available, or whether syphilis predisposes to more severe, or premature degenerative vascular disease. In one of the previous reports,[4] evidence in favor of the latter view was presented in that there were significant differences between syphilitic and nonsyphilitic patients when palpable stiffening of superficial vessels, radial, brachial, and temporal, was compared. However, validity of findings referable to palpation of vessels can be disputed because of the subjective factors involved.

OL.
4
956

TABLE I. NONSPECIFIC X-RAY ABNORMALITIES OF THE HEART AND AORTA COMPARED AMONG STILL LIVING SYPHILITIC AND NONSYPHILITIC PATIENTS

AGE GROUP	SYPHILITIC PATIENTS			NONSYPHILITIC PATIENTS			SIGNIFICANCE OF DIFFERENCE IN ABNORMALITY IN THE TWO GROUPS
	NUMBER OF PATIENTS EXAMINED	PER CENT NORMAL	PER CENT ABNORMAL	NUMBER OF PATIENTS EXAMINED	PER CENT NORMAL	PER CENT ABNORMAL	
45–49 years	26	38.5	61.5	20	90.0	10.0	P = < .01
50–54 years	16	56.3	43.3	16	62.5	37.5	P = .70
55–59 years	20	20.0	80.0	8	50.0	50.0	P = .10
60–64 years	19	15.8	84.2	10	70.0	30.0	P = < .01
65–69 years	26	15.4	84.6	16	43.8	56.2	P = < .05
70–74 years	15	13.3	86.7	14	35.7	64.3	P = < .20
75 years and over	16	6.2	93.8	8	37.5	62.5	P = .05
Total	138	23.9	76.1	92	58.7	41.3	P = < .01

BLOOD PRESSURE

In attempting to diagnose hypertensive cardiovascular disease among men ranging in age from the fifth to the ninth decades, we encountered the same problems as were described by Dublin and Marks,[7] who studied an aging insurance population, and by Gover,[8] who worked with various age groups in a rural health study. These workers found that inflexible standards of "normal" systolic and diastolic levels must be modified in order to allow for changes in blood pressure which accompany aging in the particular race and sex being studied. In meeting this problem of manometric standards, which still are being revised, the advantage of having nonsyphilitic controls from the onset of the study for comparison is apparent. Rather than to attempt a comparison of the blood pressure readings of the syphilitic patients with national averages for male Negroes of various geographic, occupational, and economic levels, we had only to compare the two groups in the study.

Fig. 1 shows the comparative percentage of syphilitic and nonsyphilitic patients having abnormal blood pressure according to the age of patients when examined in 1952. Abnormal blood pressure is defined as systolic pressure greater than 150 mm. Hg and/or diastolic pressure greater than 90 mm. Hg.

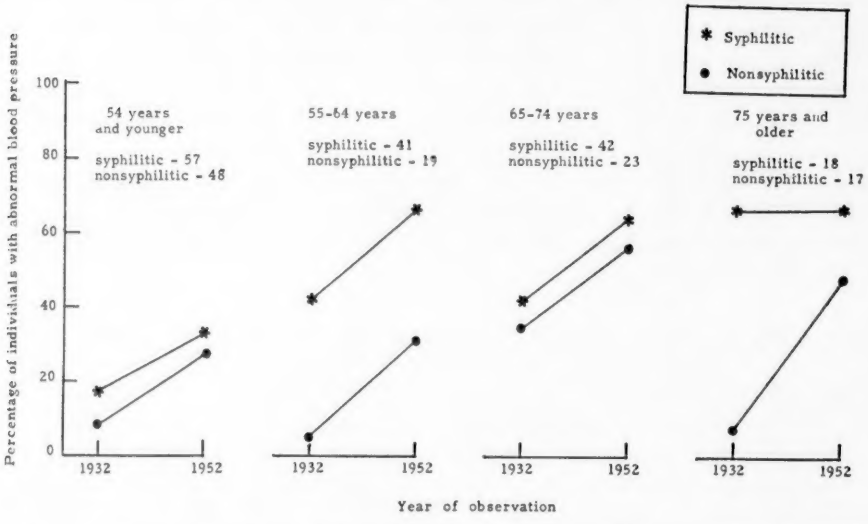


Fig. 1.—Comparative percentages of patients with abnormal blood pressure (systolic, more than 150 mm. Hg, and/or diastolic, more than 90 mm. Hg) among syphilitic and nonsyphilitic individuals examined both in 1932 and 1952, by age in 1952.

Since these percentages of abnormality are based on patients examined both in 1932 and 1952, it is apparent that there is an increasing amount of abnormality over the twenty-year span among the syphilitic and nonsyphilitic individuals in each age group. The slopes of the lines connecting the points of abnormality in 1932 and 1952 are practically identical for syphilitic and nonsyphilitic patients in the age (in 1952) intervals 34 years and younger, 35 to 44 years, and 45 to 54 years. This similarity would indicate that the slope is a true measure of the effect of aging process on the blood pressure. However, the level of the line for the syphilitic group in each of these three age groups is higher than that for the nonsyphilitic group, which would indicate a higher prevalence of blood pressure abnormality among the syphilitic patients. Since the number of patients in the last age-interval was limited to those 75 years or older when examined in 1952, the percentages are based on a small number of patients and are, therefore, not too meaningful. It is of interest, however, that among these elderly patients the same percentage of abnormality in blood pressure was found in the syphilitic group in 1932 as was found in 1952, and, for the most part, the same individuals were found to be abnormal in this respect.

ELECTROCARDIOGRAMS

As early as 1932, electrocardiograms were taken on selected patients but did not become part of the routine examination until 1938. Precordial leads have been used since 1948. In some cases serial records are available over a

twenty-year period of observation; however, in most patients they cover only the past fourteen years. From what is known of the insidious and chronic nature of syphilitic cardiovascular disease, we did not expect to obtain diagnostic electrocardiograms from the survivors. We did expect that the more advanced cases of syphilitic heart disease would show electrocardiographic evidence of cardiac hypertrophy, ventricular strain, arrhythmias, ischemic patterns, or other signs of heart damage which are nonspecific as to etiology. At the onset of the survey, we reviewed the records taken on those men who had been autopsied and for whom ante-mortem electrocardiograms were available in order to see if there was any relationship between electrocardiographic evidence of damage and pathologic changes. It was realized that the sample was small, but we were nonetheless surprised to see the lack of correlation (Table II). Despite their apparent lack of value as a screening device, ECG's were again taken routinely in the recent survey. The records were interpreted without reference to patient's syphilitic or nonsyphilitic status. Diagnosis of "abnormal record" included minor abnormalities of rhythm and axis deviation. These diagnoses were made by one of us (S.H.S.) who had only a general background in record interpretation; frequent consultations with the Veterans Administration hospital cardiologist were held. Our conservative policy was to require obvious evidence before calling any record abnormal. The patients with syphilis (Table II) not only had more abnormal records than the nonsyphilitic individuals but this difference was found to be statistically significant.

OL.
4
956

TABLE II. COMPARISON OF ABNORMAL ELECTROCARDIOGRAMS

A. Among Syphilitic and Nonsyphilitic Patients Later Examined at Autopsy

PATIENT STATUS	NUMBER OF PATIENTS EXAMINED POST MORTEM	ECG INTERPRETATION PRIOR TO DEATH			
		NORMAL		ABNORMAL	
		NUMBER	PER CENT	NUMBER	PER CENT
Syphilitic	23	19	82.6	4	17.4
Nonsyphilitic	8	2	25.0	6	75.0

B. Among Living Syphilitic and Nonsyphilitic Patients

PATIENT STATUS	NUMBER OF PATIENTS EXAMINED	ECG INTERPRETATION			
		NORMAL		ABNORMAL	
		NUMBER	PER CENT	NUMBER	PER CENT
Syphilitic	152	101	66.4	51	33.6
Nonsyphilitic	93	74	79.6	19	20.4

Our conclusion from the findings in this examination suggest that although it is not possible to ascribe electrocardiographic abnormalities to the syphilitic process alone, it is possible that the excess of abnormal findings in the syphilitic group may represent an undefined effect of the specific disease factor.

CLINICAL ABNORMALITIES

Under the general heading of clinical abnormalities are grouped various features of the medical history and physical examination. The results of this comparison are shown in Table III, which for convenience is divided into two parts, showing abnormalities which proved to be significantly different in their occurrence among the syphilitic and nonsyphilitic patients, and those conditions for which significant differences could not be established. Most of the signs and symptoms considered in this table are concerned with the cardiovascular system. This indicates not so much that our attention was focused on cardiovascular changes, but rather that relatively simple methods for recording and measuring cardiovascular abnormalities were more readily available than tests of other systems, e.g., central nervous system.

VOL 4 195

TABLE III. THE COMPARATIVE INCIDENCE OF CLINICAL ABNORMALITIES AMONG SYPHILITIC AND NONSYPHILITIC GROUPS

ABNORMALITIES	PATIENT STATUS			
	SYPHILITIC (139)		NONSYPHILITIC (93)	
	NO.	PER CENT	NO.	PER CENT
A. Abnormalities found to be significantly greater among the syphilitic group				
Cardiac—chief complaint	32	23.0	7	7.5
Cardiac enlargement	89	64.0	44	47.3
Arteriosclerosis	100	71.9	47	50.5
"Abnormal" blood pressure (systolic 150 and/or diastolic 90)	81	58.3	31	33.3
B. Abnormalities not significantly greater among the syphilitic group				
Angina	32	23.0	17	18.3
Dyspnea	71	51.1	40	43.0
Symptomatic arthritis	74	53.2	48	51.6
Strokes (cerebrovascular accidents)	4	2.9	3	3.2
Deafness (partial or total)	12	8.6	8	8.6
Impaired vision (nonsyphilitic)	8	5.8	7	7.5

Differences in the incidence of abnormalities in the two groups were considered to be significant where the t-value was 2.0 or more, or at the 5 per cent level of significance.

First, only 232 of the 267 men examined in the survey are compared in this table. This is because most of the examinations done outside of Alabama by other examiners were omitted. It was felt that some of these clinical conditions

might be evaluated differently by physicians using somewhat different criteria. Only comparable data, therefore, are included. Furthermore, these abnormalities were recorded as the men were examined, without bias or knowledge of the patient's syphilitic or nonsyphilitic status. In Table III, "cardiac—chief complaint" refers to whether the patient volunteered some pertinent symptom referable to the cardiovascular system as his chief or presenting complaint. This includes severe intermittent claudication of the extremities, angina, dyspnea, orthopnea, severe palpitation, or syncope.

However, if the patient insisted that some other symptom was more troublesome than cardiac symptoms, then he was not included in this group.

"Cardiac enlargement" includes findings from both fluoroscopic and x-ray examinations. In borderline cases where disagreements occurred in interpretation of findings, the diagnoses of physicians who had previously examined the patient were given consideration.

OL.
4
956

"Arteriosclerosis" includes evidence of degenerative vascular changes, whenever and however observed. Such evidence includes: (1) signs of sclerosis seen in the eye grounds, (2) severely reduced dorsalis pedis artery pulsations observed by palpation and recorded by graphic tracings using a tambour cuff, (3) calcified plaques seen in the aorta on chest films, (4) electrocardiographic evidence of myocardial damage occurring in younger men, (5) a good history or signs of recent cerebral vascular accidents, and (6) evidence of Parkinsonism.

"Abnormal blood pressure" refers to a fixed arbitrary standard by which syphilitic and nonsyphilitic patients could be easily compared. Any patient with a systolic reading above 150 mm. Hg and/or a diastolic reading above 90 mm. Hg was arbitrarily considered "abnormal" for Table III.

Complaints of dyspnea were much more frequent than complaints of angina; the degree of dyspnea usually being mild ("short-winded after climbing two or three flights of steps").

"Arthritis" was symptomatic primarily, although many cases were substantiated by visible changes in the extremities or by x-ray evidence.

"Strokes" were recorded whenever neurologic evidence supported the history given by the patient. Three cerebrovascular accidents which occurred among men less than 60 years of age were among syphilitic patients.

In summary, Table III shows 4 cardiovascular features in which the syphilitic patients suffer by comparison with the nonsyphilitic. Each of the 4 differences is statistically significant at the 5 per cent level of significance. At this point, it is well to reiterate that this is a study of Negro males, of whom it has been said that the cardiovascular system is peculiarly susceptible to attack by the *Treponema pallidum*.[9]

NEUROLOGIC FINDINGS

A neurologic examination was a part of the general physical examination and included an estimation of mental status, deep and superficial reflexes, examination of optic discs, coordination, gait and speech, motor and sensory functions, cranial nerves, pupillary responses, and Romberg and Babinski signs. In the

aging group of poor educational background, tests were purposely as simple and objective as possible. Although the range of normality was broad, abnormalities, when present, were striking and multiple and usually were associated with other signs.

LATE SYPHILIS

Among the 159 surviving syphilitic patients examined, 23 (14.5 per cent) showed evidence of late syphilis (Table IV). Eleven, or approximately half of these had signs of cardiovascular disease; other patients were about evenly divided between neurosyphilis and osseous syphilis. It is worth noting that the bulk of these patients were untreated and that no one patient with late syphilis had received an adequate course of therapy.

TABLE IV. EXTENT OF DEVELOPMENT OF LATE SYPHILIS BY TREATMENT STATUS IN LIVING SYPHILITIC PATIENTS AT THE TIME OF THE 1952 PHYSICAL EXAMINATION

LATE SYPHILITIC MANIFESTATION	NUMBER OF PATIENTS	UN-TREATED	PRACTI-CALLY UNTREATED	INADE-QUATELY TREATED	ADE-QUATELY TREATED
Paresis	1	—	—	1	—
Tabes	1	1	—	—	—
Optic atrophy	2	1	—	1	—
Tabes and optic atrophy	2	1	—	1	—
Aneurysm	3	2	1	—	—
Aortic regurgitation	5	4	—	1	—
Aneurysm and regurgitation	2	1	1	—	—
Tabes, optic atrophy, and aneurysm	1	—	—	1	—
Bone syphilis	6	3	1	2	—
All late syphilis (total)	23	13	3	7	—

DISCUSSION

Syphilis has indeed a serious adverse effect on the well-being of the group of individuals in whom the disease is allowed to progress with little or no treatment. The reduction in life expectancy which has been shown is in part based upon the fact that certain of the late complications of the disease either kill directly or are considered as primary causes of death as shown in members of syphilitic and control groups who have come to autopsy. Review of those still living (Table IV) reveals that an appreciable number have late complications of syphilis which probably will result, for some at least, in contributing materially to the ultimate cause of death. It is evident, though, that it is impossible in the case of the individual to predict whether the body will overcome the infection without treatment, or whether one of the late complications will develop. Indeed, it seems from consideration of the autopsy material that it is impossible during life to determine whether the untreated individual, seronegative or not, has chronic activity in the aorta as a result of the persistence of activity of *T. pallidum*.

It has been shown that in addition to specific marked changes related to syphilis, the syphilitic group also has an excess of abnormal findings not con-

sidered as directly related to syphilis. These findings cannot be explained, and the final interpretation of these data will have to be held in abeyance until the entire group has run the life span.

SUMMARY

This report is one of a series in a continuing study of untreated syphilis in the male Negro by the United States Public Health Service. The study consists of 600 men who have been followed clinically, serologically, and pathologically (to post-mortem examination in over 63 per cent of the deceased patients). This study is unique because of the inclusion of nonsyphilitic individuals of comparable ages to the syphilitic patients at the onset of the study; furthermore, these "controls" have been followed as intensively for the past twenty years as have the syphilitic men.

In this report, methods and problems in diagnosis of clinical syphilis are described as they were encountered in the collection of the statistical data obtained. Clinical findings are reported from physical examination, medical history, x-ray and fluoroscopy, serologic testing, electrocardiography, and neurologic examination; comparisons between syphilitic and nonsyphilitic individuals are shown usually by age groups; these comparisons have been subjected to statistical tests for significance.

1. Findings in this study seem to confirm the impression that, in male Negroes with untreated syphilis, the cardiovascular system frequently is involved.

2. Among the 23 living men who have developed some form of late syphilis, not one has received adequate therapy prior to the recent survey.

3. Problems of diagnosis of syphilis among the aged are complex, especially in evaluating findings related to the cardiovascular system.

REFERENCES

1. Heller, J. R., Jr., and Bruyere, P. T.: Untreated Syphilis in the Male Negro. II. Mortality During 12 Years of Observation, J. Ven. Dis. Inform. **27**:34, 1946.
2. Shafer, J. K., Usilton, L. J., and Gleeson, G. A.: Untreated Syphilis in the Male Negro. A Prospective Study of the Effect on Life Expectancy, Milbank Mem. Fund Quart. **32**:262, 1954, and Pub. Health Rep. **69**:684, 1954.
3. Peters, J. J., Peers, J. H., Olansky, S., Cutler, J. C., and Gleeson, G. A.: Untreated Syphilis in the Male Negro. Pathologic Findings in Syphilitic and Nonsyphilitic Patients, J. Chron. Dis. **1**:127, 1955.
4. Diebert, A. V., and Bruyere, M. C.: Untreated Syphilis in the Male Negro. III. Evidence of Cardiovascular Abnormalities and Other Forms of Morbidity, J. Ven. Dis. Inform. **27**:201, 1946.
5. Rosahn, P. D.: The Adverse Influence of Syphilitic Infection on the Longevity of Mice and Men, Arch. Dermat. & Syph. **66**:547, 1953.
6. Kemp, J. E., and Cochems, K. D.: Studies in Cardiovascular Syphilis. I. Teleroentgenography in the Diagnosis of Early Syphilitic Aortitis: A Comparison of Findings in 1,000 Syphilitic and 600 Nonsyphilitic Individuals, Am. Heart J. **13**:297, 1937.
7. Dublin, L. I., and Marks, H. H.: A Note on the Inheritance of Cardiovascular Disease—Results of Life Insurance Investigations, J. Mt. Sinai Hosp. **8**:482, 1942.
8. Gover, M.: Physical Impairments of Members of Low-Income Farm Families—11,490 Persons in Rural Families Examined by the Farm Security Administration, 1940. VII. Variation of Blood Pressure and Heart Disease With Age; and the Correlation of Blood Pressure With Height and Weight, Pub. Health Rep. **63**:1083, 1948.
9. Vonderlehr, R. A., Clark, T., Wenger, O. C., and Heller, J. R., Jr.: Untreated Syphilis in the Male Negro. A Comparative Study of Treated and Untreated Cases, J. Ven. Dis. Inform. **17**:260, 1936.

VOL.
4
956

Review

THE PALLIATIVE CARE OF INOPERABLE AND INCURABLE RECRUDESCENT NEOPLASMS

MURRAY M. COPELAND, M.D., D.SC.

WASHINGTON, D. C.

From the Department of Oncology, Georgetown University Medical Center

(Received for publication Dec. 15, 1955.)

THE reported cancer mortality rate in the United States for 1953 was over 229,000 deaths and is said to be increasing at the rate of 3 per cent, or about 6,000 per year. This is in part due to increased longevity in a growing population.

Steiner has shown that the total number of cancer cases within a given period is much larger than the reported death rate and includes the estimated unreported deaths, the cured cancer cases, and those incidental cancers found in individuals dying of other causes. He estimated that for the year 1948 there were at least 286,721 patients with cancer in this country. Such figures indicate the enormity of the problem which confronts us in caring for those patients who cannot be freed of their disease.

The problem is further complicated by the fact that while all cancers have in common the fundamental process of uncontrolled new growth, from other points of view they behave in different ways. On the basis of incidence, life history, causative factors, aggressive tendency, symptomatology, problems in diagnosis, method of treatment, response to treatment and prognosis, they suggest different diseases.

The estimated national percentage of cure in 1948 ranged from a high of 85 per cent for skin cancer (excluding malignant melanoma), down through 20 per cent for cancer of the breast, larynx, and uterus, to less than 1 per cent for cancers of the pancreas (Steiner). Reports from some individual physicians and clinics give better survival rates than the recorded national averages.

The primary aim in treatment of any cancer is the complete ablation of the disease. To this end various forms of treatment are employed singly or in combinations, with varying degrees of success. The cures have been largely in the localized and accessible tumors. The disseminated and less accessible tumors make up the bulk of inoperable lesions which require a palliative approach to treatment. With research, the attack on uncontrolled cancer is slowly changing the complexion of this most difficult problem. Progress, while slow, has consisted of a series of small victories, adding a few per cent here and there to survival rates. This in no way precludes, however, the possibility of sudden and dramatic advances in cancer control.

Progress in dealing with the cancer problem must not be measured solely by the cure rate, but also by the advances in palliative therapy. Gratifying progress has been made in extending useful life and rendering more comfortable patients who have inoperable cancer. Prolongation of active life up to five or more years in some patients with prostatic carcinoma by antiandrogen therapy is an encouraging mile post, and is significant because it arouses hope that, with slightly more effective therapy, cures may be achieved. The disseminated forms of cancer have proved susceptible to ablation through clinical and basic research. Nobody can predict from what source the next advance will emanate, but surely it will come.

Many disciplines have contributed to palliation, including the use of (1) chemotherapeutic, (2) endocrinologic, (3) surgical, (4) radiotherapeutic, and (5) general medical supportive measures.

VOL.
4
1956

CHEMOTHERAPY

There is no chemical compound at the present time which can cure any type of disseminated cancer, but there are chemotherapeutic agents available which are of value in the clinical management of specific neoplasms.

Treatment of malignant disease by chemotherapeutic agents, other than by endocrine therapy, is outlined as follows:

1. *Nitrogen Mustard Type Compounds.*—

a. *Nitrogen mustard*, originally a war gas, was intensively studied under the military research program of the United States Army during World War II. There are long reviews available, including discussions on inactivation of enzymes, etc. Its use clinically was predicated upon the rapid inactivation of the alkylating agents in the tissues with the clinical possibility of administering it intravenously.

The precise mechanism of nitrogen mustard action is still not known, but research studies indicate that the point of the metabolism of nucleic acids is the cellular site at which the compounds act. The toxic manifestations and pathologic changes resemble total body irradiation. Cytologic studies with the use of mustard demonstrate mitotic inhibition of cells exposed to low concentrations of the drug. The toxicity of the drug is appreciable and its safe use requires a knowledge of the toxic manifestations as well as the proper dosage and indications for its use.

Nitrogen mustard (HN_2) is injected intravenously in saline solution equaling 1 mg. per cubic centimeter and is usually given daily in a dose of 0.1 to 0.2 mg. per kilogram of body weight, not to exceed a total of 0.4 mg. per kilogram in any one series of treatments. The single lethal dose is estimated at about 1.0 mg. per kilogram of body weight. Extravasation outside the vein produces a severe local reaction. Nausea and vomiting commonly occur within a few hours after injection. Klopp and associates have utilized nitrogen mustard intra-arterially, using the principal artery leading into the tumor area. A polyethylene catheter under sterile surgical technique is introduced into the vessel and kept patent with saline and heparin. HN_2 can be injected at 8-, 12-, or 24-hour intervals up to fifteen days with a total daily dose of 3 to 6 mg. This represents a larger total dose

safely given than is tolerated intravenously. The difficulty of repeating intra-arterial therapy, the hazard of hemorrhage at the cannula site, and thrombophlebitic phenomena limit the usefulness of this method of giving HN_2.

Nitrogen mustard (HN_2) in therapeutic doses causes destruction of normal lymphoid tissue and the bone marrow. The drug has contributed principally to the medical management of the lymphomas, some of the blood dyscrasias, and bronchiogenic carcinomas.

Dramatic improvement may be noted in the treatment of generalized Hodgkin's disease by HN_2. It has not replaced the usefulness of conventional x-ray therapy for the localized disease but can be utilized as an alternative in the treatment of the generalized form of Hodgkin's granuloma. The use of nitrogen mustard in disseminated Hodgkin's disease often reduces fever, with rapid subjective improvement, reduces lymphadenopathy, bringing relief from pressure phenomena and controlling pruritus, and bone pain, thus reducing the amount of roentgen-ray therapy which may be required and shortening necessary hospitalization. About 80 per cent of patients with Hodgkin's disease may at some time or other be benefited by nitrogen mustard therapy prior to the terminal phases of the disease. The drug apparently offers no increased longevity to the patients.

The lymphosarcomas respond to nitrogen mustard in a manner similar to that noted in Hodgkin's disease. Giant follicular lymphosarcoma and small-cell lymphocytic lymphosarcoma respond most favorably to the drug. Reticulum-cell lymphosarcoma remissions follow such therapy only rarely. The life expectancy is not increased, but, in the management of generalized involvement, nitrogen mustard is a helpful addition to therapy by irradiation or other appropriate therapeutic procedures.

In acute leukemia, nitrogen mustard completely fails to produce any sort of remission.

In chronic myelocytic leukemia, response to the chemical agent has been more encouraging, especially in the early phases of the disease. As the disease progresses toward its final phases, remissions are less complete, are of shorter duration, or fail to appear.

In chronic lymphoid leukemia the response to nitrogen mustard is less predictable. Favorable responses are observed, but most investigators feel that other forms of therapy are to be preferred.

In treatment of the chronic leukemias, the relative efficiency of urethane, arsenic, x-ray therapy, radioactive phosphorus, and nitrogen mustard shows no dramatic advantage, one over the other.

From the available evidence in treating polycythemia rubra vera, phlebotomy, in conjunction with radioactive phosphorus, produces adequate subjective improvement and suppression of red cells more constantly than does nitrogen mustard.

In mycosis fungoides and Kaposi's sarcoma, a good response to nitrogen mustard therapy is noted, in some cases, for varying periods of time.

In a wide variety of inoperable or recrudescent carcinomas, nitrogen mustard has been given a clinical trial. Temporary therapeutic results have been reported in a number of cases with disseminated cancers, including uterine, ovarian, gastric, mammary and lung carcinoma, seminomas, and chorioepithelioma. Although

VOL. 4 1956

temporary regression has been sporadic and the results unpredictable in most of the malignant epithelial tumors mentioned, bronchiogenic carcinoma has responded with sufficient regularity to permit consideration of the drug in treating many cases which are inoperable. The histopathology of bronchiogenic tumors influences the response to nitrogen mustard. The anaplastic bronchiogenic carcinomas are temporarily inhibited more frequently than are the well-differentiated forms of the disease. About 75 per cent of the inoperable cases of bronchiogenic carcinoma which receive nitrogen mustard show some remission of symptoms lasting from two weeks to about two months. There is alleviation of cough, pain, dyspnea, hemoptysis, and occasionally there is roentgenographic evidence of regression of the primary lesion as well as resorption of pleural effusion. In patients with mediastinal block, HN_2 is preferred because of the hazard of giving x-ray therapy and producing increased edema. X-ray therapy may be used judiciously after nitrogen mustard therapy is under way. There is no evidence that the combination of nitrogen mustard and roentgen therapy improves the outlook in terms of immediate or long-term results.

b. *Triethylene melamine* (TEM), a nitrogen mustardlike compound, has been introduced in the past four years as a cancer chemotherapeutic agent. It closely resembles nitrogen mustard in its therapeutic and toxic activity. Its main advantages are that it is active when given by mouth, and the incidence and severity of nausea and vomiting are less than after the giving of nitrogen mustard. The evidence indicates that TEM is effective in the same group of neoplastic diseases that respond to nitrogen mustard and offers the possibility of giving maintenance doses, thereby prolonging remissions.

TEM may be given intravenously, usually in doses of 2 to 3 mg., repeated the next day. A total dose of 8 or 9 mg. within the first week or ten days rarely should be exceeded. Of advantage is the fact that it can be administered by mouth in doses of from 2.5 to 5 mg. a day not to exceed 8 to 15 mg. in any one course. The dosage must be governed by a frequent evaluation of its effect on the blood picture.

One must be extremely careful in giving this drug, due to the depressing effect on the bone marrow. Repeated blood counts and follow-up of the patient are essential during and after the period of treatment.

c. *Triethylene phosphoramide* (TEPA) and triethylene thiophosphoramide (thioTEPA) have shown some inhibiting effects on certain tumors. The former appears more toxic than the latter, causing nausea, abdominal cramps, local irritation, and hematopoietic depression. Due to the toxicity of TEPA, it has not been used extensively in the chemotherapy of cancer.

d. *ThioTEPA* or triethlene thiophosphoramide is similar to TEPA save for the introduction of a sulfur for an oxygen atom. Bateman, Shay, and associates and Zarafonetis and co-workers, have had interesting experiences with this drug. ThioTEPA may be given intravenously, intramuscularly, intra-arterially, intraperitoneally, or interstitially into the tumor. Bateman has demonstrated that much larger doses can be injected into the tumor directly than can be given by other methods (5 to 40 mg.). This modality of administration has produced a maximum effect locally and has also caused some response to distant metastatic

deposits. Intravenously the dosage should not exceed 5 to 10 mg., and extreme care should be utilized in following the blood picture before additional drug is given. Further dosage is always governed by the white count level. The maximum white blood cell depression was noted two or three weeks after a single dose of the drug. Severe leukopenia followed by thrombocytopenia was noted occasionally. Gastrointestinal upset and fever may be noted. Advanced malignant disease of the breast and ovary, in some instances, have shown subjective and objective temporary response to therapy in the hands of Bateman, Shay and associates, and in our experience at the Georgetown University Medical Center. Zarafonetis and co-workers report that chronic myeloid and lymphoid leukemia in selected cases have shown clinical and/or hematologic remissions of varied duration. They feel that thioTEPA can be added to present-day drugs as being of some value in the management of chronic leukemia.

Studies to date indicate that the phosphoramides, from the standpoint of palliative results, at least deserve further exploration.

VOL. 4 1956

2. *Urethane.*—The use of urethane or ethylcarbamate, stems from experimental observations of Haddow and Sexton on the effect of the chemical compound in animal tumors. The clinical use of urethane in man was initiated by Paterson and her associates in 1943. The first patients treated had far-advanced malignant disease and the results were uniformly disappointing, but it was noticed that in some of these patients there was a striking fall in the leukocyte count. This suggested a trial of the drug in patients with leukemia. It has not favorably affected the course of acute leukemia but is a satisfactory therapeutic agent in producing temporary remissions in the chronic leukemias. It more consistently brings about remissions in the myelocytic than in the lymphocytic form of leukemia. No obvious advantage of the drug over x-ray therapy or radioactive phosphorus can be claimed, and many observers prefer the latter drug. The effect of urethane in multiple myeloma has proved beneficial in a number of cases (35 per cent). Stopping the therapeutic agent with the remission of symptoms and readministration of the drug when symptoms reappear has been temporarily successful. There is no final evaluation as to whether the drug increases longevity, but it appears to be the best chemotherapeutic agent available for temporarily controlling multiple myeloma. The dosage of urethane varies from 1 to 5 Gm. every twenty-four hours. Few patients can tolerate doses much above 3 Gm. per day. It is well known that there are toxic effects in using urethane. Anorexia, nausea, and vomiting due to gastrointestinal irritation may be encountered. Sedation effects and suppression of bone marrow are also noted with massive dosage. Aplasia of the marrow, while rare, is dangerous and is difficult to anticipate. It is advisable to determine the blood count at weekly intervals, during dosage by urethane. If rapidly occurring anemia develops, the drug should be stopped and the patient carefully followed for the possibility of a developing pancytopenia.

3. *Folic Acid Antagonists.*—The introduction of folic acid antagonists into cancer therapy was predicated upon the fact that the function of folic acid is intimately associated with cell growth, as in the bone marrow. This suggested that folic acid analogues might be effective in controlling cellular growth. Re-

search and clinical trial formed the basis for the use of antifolic drugs in acute leukemia. Sidney Farber and associates, at the Children's Hospital in Boston, introduced the antifolic drugs and found that they produced dramatic results in acute leukemia in children. Continued trial, however, revealed that only a third of the cases responded fully, with an additional group showing symptomatic improvement and some hematologic response. The remissions proved to be temporary, but the use of the drugs has extended the survival time, in children who do respond, up to approximately twelve months. Only two of the folic acid analogues have been extensively employed: Aminopterin and A-methopterin. Both drugs are toxic, but the latter is less so. The dosage of Aminopterin is 0.5 to 2.0 mg. per day, given either intramuscularly or by mouth. A-methopterin is given orally in doses ranging between 2.0 and 5.0 mg. per day. Dosage is started with a minimal amount of the drug and gradually increased until a marked depression of the normal and abnormal cells of the blood and bone marrow is noted, or until other unrelated toxic manifestations occur. Following the induction of a remission, maintenance therapy should be given, avoiding toxic complications. Chronic leukemias have not been observed to be favorably influenced by the antifolic compounds. An occasional case of lymphosarcoma and malignant melanoma have shown some temporary response to these drugs, but because of the marked toxic hazard the therapeutic use of these agents in far-advanced disease is not recommended.

4. *The Compound 6-mercaptopurine.*—This new purine antagonist is the product of a program in the laboratories of the Sloan-Kettering Institute. The substance, though not curative, is useful in the treatment of acute leukemia and in some cases of chronic leukemia. Metastatic carcinoma, sarcomas, Hodgkin's disease, lymphosarcoma, and chronic lymphatic leukemia have not responded to 6-mercaptopurine. It has now been in general use since Jan. 23, 1953. The remissions caused by the drug are temporary, lasting from two to eight months, and resistance develops rapidly. 6-mercaptopurine has been administered almost entirely by mouth, the usual dosage being 2.5 mg. per kilogram of body weight daily, with little evidence of toxicity. Higher doses in children and adults may bring about severe marrow cell depression and gastrointestinal disturbances. There appears to be, however, little or no cross-resistance between 6-mercaptopurine and the folic acid antagonists or cortisone. When the patients become resistant to 6-mercaptopurine, they may still respond to the antifolic drugs and cortisone, and vice versa. The technique of inhibiting a number of enzyme systems by combination therapy in sequence appears to be an important facet of chemotherapy in the future.

5. *Myleran, or GT-41.*—This sulfonic acid ester has been found to produce pronounced depression of granulopoiesis in rats and in man. This compound 1,4-dimethanesulfonyloxybutane, unlike roentgen rays or the amine mustards, does not appreciably depress lymphopoiesis. Galton and associates, Wintrobe and co-workers, Petrakis and associates, and others have found that Myleran has a favorable effect upon patients with chronic granulocytic leukemia. It appears to be ineffective in acute leukemias and in chronic myeloid leukemia in myeloblastic relapse.

Many dosage schedules have been tried, but recently Galton and Till have indicated their administration of the drug has been in the form of 2 mg. and 0.5 mg. tablets orally. The standard dose for adults since August, 1951, has been 0.06 mg. per kilogram of body weight on a daily basis. The treatment has lasted from three to seven months. Retreatment after such courses was deferred until symptoms returned (five to eighteen months later) or unless the platelet count exceeded 800,000. Remissions following subsequent courses were found to be shorter than after the first, none exceeding one year. Because remissions were shorter following second and third courses of Myleran, Galton and Till began maintenance doses in such patients (six in number), using from 0.5 to 4 mg. daily. In eleven other patients, maintenance therapy was given immediately after an initial period on standard dosage.

The dosage required for maintenance varied from patient to patient and in the same patient at different times. No patient has received continuous therapy longer than twenty-three months. Specific resistance in three patients suggested that it will not be effective indefinitely. Dangerous thrombocytopenia has not developed since small doses have been used. Although the leukocyte count is a sensitive index to the activity of Myleran, the hemoglobin level is a more valuable guide as to its efficacy. A hemoglobin increase is noted for twelve to twenty weeks and is then maintained for variable periods of time. Galton recommends a follow-up each two weeks or at monthly intervals when not more than 0.06 mg. of Myleran per kilogram of body weight daily is being given. The general condition of the patient and the status of the blood is carefully followed so that therapy may be reduced or stopped as necessary.

Beneficial results from Myleran therapy are characterized by a feeling of well-being, relief of anemia, decrease in liver and spleen size, return to normal in platelet count and differential leukocyte count, and decrease in hemorrhagic manifestations.

In the patient whose disease has become "radio-resistant," Galton and Till feel that Myleran has produced benefits that radiotherapy (including radioactive phosphorus) could not offer. They have treated some thirty-one patients with chronic myeloid leukemia by the use of Myleran and indicate that its chief advantage is its efficacy when radiotherapy has been of limited value or has ceased to be effective. It was felt that the drug was superior to urethane and arsenic. While they have not used TEM, they suggested that the results from Myleran are superior, according to published reports.

ENDOCRINE THERAPY

An increasingly large body of knowledge brought about through research and clinical trial has crystalized the significance of hormones as regulators of growth processes through their actions as modifiers of cellular enzymatic reactions. A more direct relation to cancer is apparent in the effects of increased clinical administration or withdrawal of selected steroids on certain malignant tumors in the human being. At the present time, sex hormones are widely used in the treatment of carcinoma of the prostate and breast.

1. *Antiandrogen Therapy.*—In carcinoma of the prostate, the largest group of patients seen in clinical practice constitutes those in whom the lesion is in-

VOL. 4 1956

operable, with metastases. Colston, Brendler, Sullivan, and Hartwig have re-evaluated certain of the borderline cases where the tumor has penetrated beyond the capsule and has become fixed, but without metastases. Following endocrine therapy some of these lesions regress in size and are being removed. The results of this study await further evaluation.

In treatment of prostatic carcinoma with metastases, knowledge of endocrine control is based largely on the studies of Huggins and also of Herbst. Neither orchiectomy nor estrogen therapy is fully ideal. The inhibition of androgens by diethylstilbestrol is not complete and the former is effectively depressed only while treatment is being employed. Many investigators feel that five-year control of inoperable prostatic carcinoma is most effectively obtained by the concurrent use of orchiectomy with estrogen therapy as the primary form of treatment, while others reserve castration for subsequent therapy to be used only when reactivation of the tumor becomes apparent. Carroll and Brennan report that combined therapy in fifty-three patients gave a longer period of survival than is obtained by either orchiectomy or estrogen therapy alone.

A large variety of estrogens is available for the palliation of prostatic cancer. The one most widely employed is diethylstilbestrol (1 to 5 mg. daily). Ethinyl estradiol in daily doses of from 0.15 to 3 mg. may be used for several weeks with gradual reduction in dosage. Estrogen therapy can produce gynecomastia and complete impotence with disappearance of semen and often causes annoying degrees of nausea and salt retention when given in larger doses. Bilateral scirrhous carcinoma of the male breast has occasionally been reported from prolonged use of estrogen but it is open to serious question as to whether the breast lesions may not be metastases from carcinoma of the prostate. Castration also has disagreeable features. It is costly and may create some psychosomatic disturbance.

The necessity for giving a sufficient dosage of estrogen in treating prostatic carcinoma bone metastases must be stressed; an insufficient dose will yield no results. The average length of time necessary to observe healing of metastatic bone lesions radiographically is from three to six months. Bone pain relief may be early and dramatic. A drop in the serum acid phosphatase indicates inhibition of tumor activity. There may be an elevated serum alkaline phosphatase which, in the absence of liver disease, indicates an increase in reparative bone reaction. The roentgen picture of bone response does not always parallel the clinical picture. A patient showing systemic improvement may reveal a progression of metastatic bone lesions.

The greatest problem is seen in patients who undergo reactivation of carcinoma after castration and while estrogen therapy is being carried out. Whatever the cause, androgen independence or the possibility that androgen hormone is being produced from another source, the condition of the patients rapidly deteriorates. Huggins in 1951, realizing that the adrenal cortex can liberate androgenic steroids, began the treatment of a series of cases by doing bilateral adrenalectomy with cortisone substitution therapy. The prerequisite for the operation was failure of the antiandrogen control regimen. The early results were encouraging. Evidence has accumulated that bilateral adrenalectomized patients can be sustained after the operation by the use of cortisone. The remissions following adrenalec-

tomy for disseminated prostatic cancer last from three to nine months and result in relief of pain. Regression of carcinomatous lesions and cancer activity as determined by acid and alkaline phosphatase studies is rarely observed. Where exacerbation follows bilateral adrenalectomy, occasionally reinstitution of estrogen therapy will bring about a temporary remission.

Recrudescent prostatic cancer has been treated by cortisone or hydrocortisone and estrogen with some subjective benefit. It does not appear to influence the tumor growth.

The use of chlorotrianisene (TACE), a long-acting, synthetic estrogen substance according to Carroll, Brennan, Smith, Rush, and Evans, has yielded excellent palliative results with fewer side effects and a longer survival period (three-year survival rate, 70 to 80 per cent).

Carcinoma of the male breast, a rare disease, often becomes disseminated before it is discovered and before adequate therapy can be instituted. Radical mastectomy is the treatment of choice in the clinically curable group. Orchiectomy may have definite palliative value. Treves has proposed orchiectomy, alone, for breast cancer in elderly men who are poor operative risks, because the procedure is less hazardous than radical mastectomy. He reports one patient 85 years old, living four years and five months following treatment by castration alone.

VOL 4 195

There is a considerable difference of opinion as to the value of estrogen in treating male breast carcinoma. Adequate studies are not available for statistical analysis, but remissions of up to three years have been reported. Estrogen therapy occasionally may accelerate carcinoma of the male breast.

It has not been established whether estrogen therapy should be started coincidentally with orchiectomy in treatment of male breast carcinoma, but Herrmann feels that orchiectomy is the best method of changing the hormonal environment of tumor cells in male breast cancer with widespread symptomatic metastases. Marshall and Hare report that estrogenic therapy brought about regression of bone metastases in a male; while Treves notes that in two cases it failed to inhibit the growth of the tumor after reactivation of the disease.

2. *Estrogen and Androgen Therapy in Female Breast Cancer.*—Inoperable or recrudescent carcinoma of the female breast may be favorably affected by either androgen or estrogen therapy or by their withdrawal. Even though the mechanisms of action are poorly understood, the clinical use of these hormones is justified on the basis of the subjective improvement that follows in approximately 50 per cent of the cases. In 20 to 50 per cent of the patients, tumor regression is evident through observation of healing of ulcerating soft part lesion and roentgenographic evidence of reduction in metastatic lung shadows and radiolucent areas in bone, as well as improvement in marrow function.

The choice of either estrogens or androgens depends on the endocrine status of the patient. The use of estrogens during the premenopausal period, or within five years after cessation of the menses, frequently accelerates tumor growth. The evaluation of the endocrine status should be adequate before hormone therapy is carried out. The absence of menses for five years is not sufficient evidence of cessation of ovarian activity. If vaginal smears studied for one month show

absence of cornification, the administration of estrogens is permitted. If, however, evidence of estrogen activity is still noted in the vaginal smear preparations, the use of estrogens should be considered with caution and androgens are to be preferred. Breast tumor growth is not accelerated in the female with the use of androgenic hormones, but there is often lack of control of the cancer.

Estrogens are often effective in elderly women. They are particularly indicated when soft part metastases are present and bone metastases are minimal or absent, and when there is no evidence of ovarian function. In selected cases, estrogenic therapy may be followed by general subjective improvement, relief of bone pain, regression of breast, pulmonary and lymph node metastases, but rarely of abdominal visceral involvement. Huseby noted that regression of the metastatic and/or recurrent metastases from breast carcinoma occurred more frequently when the superficial soft tissues were involved than when other portions of the body were affected. Measurable regressions were noted in 55 per cent of forty patients who had metastatic disease involving the skin, subcutaneous tissues or superficial lymph nodes, following surgical intervention. In thirty-four patients with either pulmonary or pleural disease, 32 per cent showed a major regression of their lesions, and responded no differently than did those with superficial soft tissue disease.

In metastatic bone involvement, repair of bone is noted in a small percentage of cases where estrogen is used. The bone lesions progress in many instances where the superficial soft part lesions show regression.

Combined estrogen and testosterone therapy in the postmenopausal patient has at times proved effective.

A number of natural and synthetic female hormones have been used but there is no evidence of greater efficacy of one over the other (stilbestrol, ethinyl estradiol, estradiol dipropionate). Stilbestrol has been employed most frequently, with a dosage of 15 mg. daily by mouth. Such dosage should be continued for six weeks or longer to determine the beneficial results which may be obtained. If a favorable response is noted, the therapy should be continued until the lesions again show growth potential. Reactivated tumor growth may again regress following withdrawal of the hormone.

The problem of uterine bleeding while patients are under active medication is minimal. Withdrawal bleeding occurs in about 50 per cent of the patients, lasting from five to ten days. If vaginal bleeding occurs during treatment, increasing the dosage of estrogen may bring about a cessation of flow. Persistent bleeding requires stopping the therapy for two weeks or more, followed by a retrial of the therapy. Larger doses of estrogen seem to give much less bleeding during the treatment period than the small doses sometimes used for menopausal symptoms.

Nausea and general malaise may accompany the treatment and, especially in older women, retention of body fluids may cause cardiac embarrassment.

Experimentally, Hertz has given large doses of injectable estrogen intravenously, but to date has estimated only the feasibility of massive parenteral estrogen administration and the justification for further experimental exploration of massive estrogen therapy.

The administration of androgens in breast carcinoma is indicated, especially when bone metastases are sufficiently numerous and so widespread that irradiation cannot be used effectively. Symptomatic osseous metastases give the best clinical response with relief of pain (80 per cent), though often roentgenographic evidence of bone healing is not observed. Soft part metastases may be favorably influenced but with less consistent effects as compared with estrogen therapy. About 20 per cent of patients with bone metastases show definite objective improvement, while an occasional improvement in soft part metastases is seen. Prolongation of life, in terms of months or years, may be noted but, statistically, is of little significance. Testosterone propionate and methyl testosterone are the two androgenic substances which have been largely employed. Testosterone propionate is given intramuscularly in doses of from 50 mg. to 100 mg., three times per week, for a period of six to ten weeks or longer. The dosage of methyl testosterone ranges from 50 mg. to 200 mg. daily by mouth for a similar period. Arrhenomimetic phenomena are usually seen in the higher dosage ranges following such periods of treatment, but are of no vital consequence under the circumstances. In our experience, many patients will tolerate 75 to 100 mg. of testosterone propionate per week for a considerable period of time as a maintenance dose. We have observed a maximal effect from the use of testosterone propionate when combined with castration and/or roentgen therapy given over the bony metastases. An elevated serum calcium at the onset of androgen therapy or evidence of damaged kidneys is an indication to proceed cautiously. If the serum calcium returns to a normal level, the therapy will usually be satisfactory. If the serum calcium remains elevated or if a previously normal or low serum calcium level becomes unduly elevated, androgenic therapy should be terminated for a period of time. Patients with pretreatment hypercalcemia should preferably not have sex hormone therapy. Cortisone may reduce the calcium level in some of these patients. Those who are bedridden or whose renal function is markedly impaired should be treated cautiously. Frequent blood chemistry and kidney function tests should be performed. Adequate fluid intake is imperative. It is advisable to warn the patient of the more common side effects of such therapy as hirsutism, hoarseness, increased nervousness, and frequently an increased libido. After testosterone therapy is begun, relief of symptoms is frequently preceded by an exacerbation of bone pain during the first forty-eight hours. A small number of patients will not tolerate androgen therapy, showing early evidence of water balance disturbance, with nausea or vomiting or persistent and severe bone pain.

Bilateral adrenalectomy has induced significant and prolonged regression of extensive mammary cancers in some women who have not responded or ceased to respond to testosterone therapy and/or oophorectomy. It would appear that not all breast carcinomas are endocrine dependent. Prior successful trial of testosterone and/or oophorectomy in treating breast carcinoma is important as an indication of the potential success of adrenalectomy. Occasionally adrenalectomy is successful in the face of failure to control the disease by testosterone or oophorectomy.

VOL.
4
1956

Urinary calcium excretion studies (Pearson) are also of great importance in determining the desirability for doing adrenalectomy in breast cancer patients with bone metastases. Patients with a quantitative increase in urinary calcium, reflecting negative calcium balance, are the patients who usually show a satisfactory response.

The benefits of adrenalectomy in terms of tumor inhibition may be due simply to a nonspecific alteration in the hormonal environment of the body. There may be a quantitative as well as qualitative difference in the hormone environment of patients with breast cancer as compared with normal individuals. In selected cases, therefore, bilateral adrenalectomy for advanced carcinoma of the breast may give temporary striking subjective improvement and, in a few patients, evidence of tumor inhibition as well as subjective response to treatment. The modality of therapy, however, is still in the experimental stage and should be reserved for those centers adequately prepared to attack this phase of the problem.

It seems appropriate, because of the frequency and magnitude of the problem, to sum up the palliative measures which may be used in handling advanced and metastatic breast carcinoma. At the present time there are three principle palliative measures available, namely: (1) surgery for localized lesions; (2) irradiation; and (3) hormone therapy. A fourth measure includes ablation of ovarian function and also bilateral adrenalectomy when indicated.

Testosterone therapy and ablation of ovarian function is the method of choice in premenopausal women, regardless of the extent of disease distribution. In women five or more years past the menopause, estrogen therapy is best used for soft part and lung metastases. The response to testosterone propionate does not appear to depend on the physiologic age of the patient and may be used to equal advantage in treating bone metastases in elderly women. An additional advantage includes controlling subjective symptoms, such as pain.

The effective minimal total dose of diethylstilbestrol appears to be about 4 Gm., if tolerated, given over a period of three to six months. For estradiol dipropionate, the minimal total dose is estimated to be 200 mg. given over a period of three to six months, if tolerated. These hormones may be given until reactivation of the disease occurs. Cessation of therapy may bring about another remission of the disease. Shifting hormone therapy from one kind to another may occasionally bring about successive favorable responses. Side effects of the drugs must be watched for, evaluated, and corrective measures taken. Proper evaluation of the patient should precede the decision to perform adrenalectomy.

3. *Adrenocorticotropic Hormone (ACTH) and Cortisone.*—In Hodgkin's disease and lymphosarcoma, ACTH and cortisone do not control the disease process. The hormones may, however, modify the course of the illness when the patients show marked depletion, either from the disease or from the effects of roentgen therapy or nitrogen mustard administration. The temperature falls, blood elements improve, and general well-being occurs. This is only a temporary expedient, however, for when the drug is discontinued the symptoms recur. Significant temporary improvement is noted in the leukemias of childhood and in adults following the use of these hormones. Care must be used in giving ACTH or cortisone because of the side effects which accrue from their use.

Many chemotherapeutic agents which we have not mentioned are being used in an attempt to control cancer. Some of these are worthless but some have shown slight temporary effect on the course of various neoplastic diseases. The medical profession must be ever vigilant to prevent the public from being misguided by enthusiastic but ill-founded reports and from unorthodox cancer remedies. Careful scrutiny of reports and results of treatment by any therapeutic procedure for malignant disease should be resorted to before using such procedure. The Cancer Institute of the United States Public Health Service or the American Cancer Society, Inc., can often give information on whether or not unfamiliar remedies represent an orthordox approach to treatment.

PALLIATIVE SURGERY

Surgery is one of the chief methods for the ablation of this dread disease. Knowing that surgery and irradiation therapy can cure no more than 25 per cent of cancer patients, the physician must assume the responsibility of deciding when a case is possibly curable or whether surgery or irradiation can offer only palliation in terms of prolonging life, alleviating pain, or temporarily returning body function to a relatively normal status. Each individual case must be evaluated on its own merits. No general rules can be laid down for palliative surgical procedures. The field of curative surgery has been greatly extended in the past decade through the advent of antibiotics, better knowledge of electrolyte balance, fluid and blood replacement, and substitution hormone therapy. By the same token, surgical measures offer the surgeon the opportunity of carrying out significant palliative measures. Many times the surgical attack on cancer, with intent to ablate the disease, leads only to temporary palliation. Prolongation of life is an important objective in submitting a patient to surgery even when metastatic involvement is present. If the proposed operation only relieves the patient of suffering and distress, it is to be recommended. The surgeon, however, must weigh the unhappy possibility of shortening life without the benefit of palliation against the alternative of nonsurgical palliation.

It is impossible to cover the entire range of possible surgical palliative procedures, but a few of the more important and practical procedures will be mentioned:

1. Oophorectomy and/or adrenalectomy, bilateral, in advanced cancer of the breast.
2. Orchiectomy and/or adrenalectomy, bilateral, in carcinoma of the prostate.
3. Simple excision, in selected cases, for fungating, uncontrolled carcinoma located in breast, about face, groin, etc.
4. Resection of various parts of the GI tract with re-establishment of a functional lumen in the presence of metastases.
5. Neurosurgical procedures for relief of pain such as chordotomy, posterior rhizotomy, ablation of sensation in various branches of the sensory nerves.
6. Fixation of certain pathologic fractures of bone following metastases. Smith-Petersen nails or related devices about the femoral neck, and intramedullary fixation by metal pins in the long bones have proved effective, in addition

VOL. 4 1956

to the use of roentgen therapy. Appropriate casts or traction apparatus may also be used for fixation.

7. Decompression laminectomy.

8. Amputation of extremities for uncontrollable, painful and/or fungating neoplasms.

9. Removal of certain organs containing uncontrollable primary cancer for palliation and temporary inhibiting of metastatic growth, such as kidney, bowel, thyroid lesions, etc.

10. Selected resection of regional lymph nodes with metastases to prevent fungation and/or painful and crippling edema, whether or not the uncontrolled primary tumor can be found.

11. Tracheostomy for inoperable obstructive lesions about the oral cavity, pharynx, larynx, and neck.

12. Gastrostomy, gastroenterostomy, ileostomy, or colostomy for inoperable obstructive lesions involving the esophagus, stomach, and bowel.

Operative procedures which are more controversial from the standpoint of cure or palliation of malignant disease include:

1. Multiple organ excision.
2. Total gastrectomy for carcinoma of the stomach.
3. Quarterectomy.
4. Supraradical mastectomy.
5. Pancreatic duodenectomy.
6. Second look operations.
7. Pelvic evisceration—including cystectomy.
8. Hypophysectomy for breast cancer.

There is a rising tendency on the part of the surgeon to attempt the wellnigh impossible to restore the terminal cancer patient to health. A stormy postoperative course followed by a tedious and difficult convalescent period at home often awaits the patient and then ultimately a trip back to the hospital for terminal care. The surgeon must bear the responsibility of ignoring the anatomic and physiologic implication of "supraradicalism" in an attempt to cure cancer or to achieve palliation.

PALLIATIVE RADIATION

Radiation is one of the most important therapeutic agents that we currently have against inoperable cancer. The use of ionizing radiations covers a wide variety of sources and methods of application.

Radiation Therapy Sources and Methods*

A. EXTERNAL IONIZING RADIATION:

1. X-rays with energies of from 50,000 to 3,000,000 volts.
2. Gamma radiation from radium, cobalt (Co^{60}), and cesium (Ce^{137}).
3. Rotation beam therapy.
4. Multiple portal or cross-fire irradiation.
5. X-ray grid therapy.
6. Electron, proton, and neutron beams.

*Adapted from Chamberlain, R. H.: Radiation Therapy in Cancer, Proc. of Second National Cancer Conference *1*. 40. 1952. Am. Ca. Soc., Inc., N. Y., 1954.

B. INTRACAVITY RADIATION:

1. Radium or radon in appropriate applicators.
2. Artificial radioisotopes as cobalt (Co^{60}), phosphorus (P^{32}), or sodium (Na^{24}) in appropriate applicators.
3. Radioactive colloidal gold (Au^{198}).

C. INTERSTITIAL RADIATION:

1. Radium, radon, radioactive cobalt needles.
2. Radioactive cobalt in nylon tubes (used as long sutures through tumor).
3. Collcidal isotope: gold (Au^{198}).

D. INTERNAL RADIATIONS GIVEN BY MOUTH OR PARENTERALLY:

1. Phosphorus (P^{32}).
2. Iodine (I^{131}).
3. Sodium (Na^{24}).
4. Colloidal gold (Au^{198}).

A. Ionizing radiations produced by x-ray tubes may be used as an external source for irradiating tumors within the body. The energies available today vary from 50,000 volts to 3,000,000 volts. Portals of treatment and energies used vary with the site and type of lesion present. Portals may vary from 1 cm. to those which encompass the entire body.

Rotation beam therapy permits the treatment of a lesion with large quantities of ionizing irradiation but with much less skin dosage. This is accomplished by the use of equipment which rotates the x-ray tube or rotates the patient in such a way that the tumor-bearing area becomes the axis about which the patient or the tube rotates.

X-ray grid therapy has been devised so that the skin is irradiated through a metal grid with small evenly spaced circular perforations in a "checkerboard" fashion. This permits a larger total dosage of irradiation through single portals without irreparable damage to the skin and with a greater effective (depth) tumor dose.

Other external sources of ionizing irradiation include telecobalt (Co^{60}) and cesium (Ce^{137}) therapy, radium or radon packs.

The properties of radioactive cobalt make it a suitable isotope for external and interstitial radiation therapy. Its only disadvantage as compared with radium is the shorter half-life (5.3 years) of the radioactive cobalt. The advantages include the low-energy beta radiation which can be screened easily; the gamma radiation of radio-cobalt is almost homogeneous; there are no contaminating daughter-products to be considered; it is rapidly eliminated from the body; it is readily produced in the nuclear reactor in any desired quantity; it can be prepared in any shape or form; it can be electroplated on any material, subsequently being activated for clinical use; it is readily soluble, therefore can be placed in thin-walled containers or other applicators for interstitial or intracavity use; irregular volumes can be more readily implanted because of flexible nylon applicators that can be used; it costs much less than does radium and, behind a magnetic metal, it can be handled with an electromagnet.

Cesium (Ce^{137}) has a half-life of 37 years and emits both beta and gamma irradiation. Because of its abundance in the present atomic energy operations being carried on in the United States, investigations have been under way to

VOL 4 195

successfully utilize cesium as a substitute for radium and cobalt as an external source of ionizing radiation. Considerable progress has been made in this undertaking.

Betatron sources of high energy are being given a clinical trial in a few clinics.

B. Sources of ionizing irradiation to be inserted in the body cavities by suitable applicators or applications usually include radium or radon. More recently, radioactive cobalt (see under A) and other isotopes, such as radioactive gold, have been made available for this purpose. This method of application has a wide range of usefulness in the vagina, cervix, uterus, nasal passages, thoracic cavity, etc.

C. Interstitial irradiation, by means of needles or seeds containing radium, radon, cobalt, and such radioisotopes as colloidial radioactive gold, may be introduced into the tumor-bearing area.

D. Internal radiation by means of radioactive isotopes in a therapeutic capacity is complicated by a variety of factors. The biologic effect varies with the characteristic radiations of each element, and the ability of the tissue for selecting the element or compound limits the amount of isotope absorbed. Unfortunately, so far, special localization of parenterally injected or orally ingested radioisotopes has been possible mostly in normal tissues.

While radiation therapy may be curative in many cases, it also provides irreplaceable palliative relief to many patients. In the palliative care of malignant tumors irradiation is of prime importance for: (1) relief of pain and discomfort; (2) reduction in tumor size; (3) prevention of, or treatment of pathologic fractures; (4) healing of ulcerations; (5) control of hemorrhage; (6) favorably affecting the course of lymphomas and many of the blood dyscrasias; (7) causing tumor growth restraint in disseminated cancer; (8) bringing about indirect hormonal effects, such as ovarian castration; (9) prolongation of useful life; and (10) improving the mental outlook of the patient.

Radiation therapy should never be given when it is obvoius that no benefit will be achieved or actual harm may result. Patients near death usually will not benefit because of the time delay in effecting beneficial palliation after treatment begins. Severe debility, cachexia, and anemia mitigate against favorable response to treatment. A correction of these findings by supportive measures may salvage many of these patients for appropriate radiation treatment.

Certain tumor types and anatomic locations often preclude possible favorable effects from irradiation. Notable examples are: adenocarcinomas of the gastrointestinal tract, osteogenic sarcomas of bone, neurogenic sarcomas and many other forms of sarcoma, malignant melanoma, brain tumors of adult gliomal types, and acute leukemia. Irradiation over the upper abdomen is apt to produce severe nausea which, at times, vitiates any possible good one may do the patient. The lack of specificity in the localization of radioisotopes in tumor-bearing areas largely defeats their use in palliating cancer.

Great care in judgment must be exercised when considering the re-irradiation of an uncontrolled tumor. The physical factors and total dosage of the previous radiation must be known. The patient may have had treatment to the point of tolerance. Here the risk of severe tissue damage is great and will not yield any

possible gain in palliation. If the previous treatment was inadequate or minimal, further irradiation may be indicated.

Many attempts at curative irradiation become palliative in the end. The radiotherapist must carefully evaluate the patient's problem before proceeding with therapy. Palliative treatment often does not require the concentration of dosage that is necessary to completely destroy a localized cancer. With moderate dosages of irradiation, relief of bone pain and healing bone defects in metastatic cancer, and the suppression of disseminated disease from a variety of primary tumors, such as cancer of the breast, thyroid, and kidney, are considerable medical achievements. Significant palliation in treating inoperable local tumors, lymph node metastases, inoperable bronchiogenic carcinoma, pulmonary metastases, relatively localized lymphomas, and chronic leukemia, emphasizes the importance of radiation therapy.

High energy irradiation therapy (x-ray, radium, cobalt^{60}) from external sources has added some degree of palliation not possible with the lower voltages. The advantages are principally related to better depth dose with less skin reaction and less radiation sickness for comparable depth doses. In the majority of instances, however, *250 Kv. x-ray therapy* is entirely adequate as an external source for ionizing radiations.

Combined radiation therapy and surgical treatment of technically inoperable cancer has been a hopeful concept of the oncologist. In such cases the combination of radiation therapy and surgical treatment is essential, the irradiation converting a fixed fungating inoperable lesion into a resectable one. In many such cases, palliation only may be obtained but, in a few individuals, long-time survival without disease is accomplished.

Ingested and parenterally given radioisotopes depend upon the neoplastic tissue for effective selective concentration. Radioactive phosphorus and iodine at the present time represent the important radioisotopes which have practical application in parenteral or oral palliative cancer therapy. Among others which have been used are radiosodium (Na^{24}), and radiogold (Au^{198}). The latter has also been used interstitially and in body cavities.

Radiophosphorus has been a useful agent in the treatment of chronic myeloid and chronic lymphatic leukemia and polycythemia rubra vera. It is administered orally or intravenously in doses of about 75 to 100 μc per kilogram of body weight, either as single or in divided daily doses. The acute leukemias show little favorable effect and are frequently made worse. Only in an occasional case of sensitive, generalized lymphosarcoma does it appear to be useful and seldom does P^{32} favorably affect a case of Hodgkin's disease, or plasma cell myeloma. In carcinoma of the breast metastasizing to bone, relief from pain and in some cases regeneration of bone in the affected areas have been noted where radioactive phosphorus and testosterone have been administered together. J. R. Maxfield, Jr., of Dallas, Texas, has orally reported a considerable experience in the use of these combined agents. At the Georgetown University Medical Center we are carrying out a detailed study by using this method of treatment.

The limitations, however, in the use of P^{32} are inherent in the marrow differential pick-up of the element between normal rapidly dividing cells and proliferating tumor cells. Thus the bone marrow is one of the great limiting factors in the usefulness of P^{32}.

The circumstances are far different in the use of *radioactive iodine* (I^{131}) where the thyroid tissue has a specific avidity for iodine. Unfortunately, clinical experience in the treatment of thyroid cancer has shown that less than 50 per cent of thyroid cancers concentrate demonstrable amounts of iodine (I^{131}). Fewer than one in four patients with papillary cancer (the commonest form) will retain I^{131}. The tumors most resembling normal thyroid, with formation of follicles containing colloid, are the more likely to absorb significant amounts of radiotagged iodine. The more malignant forms, giant and spindle cell and anaplastic tumors, may show no evidence of iodine concentration. The uptake of radioactive iodine is unpredictable, however, from histologic evidence alone. There also may be great variation between the concentration of iodine in functioning tumors and the surrounding normal gland, as well as in various ones of the distant metastases. The competition of normal thyroid tissue must be removed by total thyroidectomy in the palliation of metastatic thyroid cancer. By so doing, a certain percentage of metastases will develop an increased avidity for I^{131}. This concentration in metastatic disease may be further enhanced by the administration of thyrotropic hormone, or by the prolonged administration of thiouracil in the totally thyroidectomized patient. Dosages by mouth usually vary between 5 to 100 mc. of I^{131}, depending on the location, extent, and functioning quality of the metastases. Rawson recommends that the dose of total body irradiation should not exceed 500 rep (roentgens, equivalents physical). Despite the limitations of the use of I^{131}, there are instances of marked palliative effect with healing of bone metastases and relief of pain. Metastases to the lungs may recede or disappear completely. No cured cases have been noted from this modality of therapy.

Radioactive sodium has not been used extensively in therapy because of the generalized distribution of sodium in the body, lack of concentration in the regions of rapid growth or cell division, and the short half-life of the radioiostope. Evans and his associates pointed out that the method appeared to be adaptable to chronic myelogenous leukemia, chronic lymphatic leukemia, polycythemia vera and other radiosensitive generalized diseases, but, due to the source of supply, the intensity of the emanation, and the necessarily frequent handling of such emanation by professional personnel, it is not feasible to use Na^{24} on a large scale for clinical therapeutic application.

Radioactive colloidal gold given intravenously has been shown to produce uniform and consistent remissions of chronic leukemia in human beings, both in the lymphogenous and myelogenous forms of the disease. More emphasis, however, has been placed on its use as an interstitial form of therapy, or within the pleural or abdominal cavity for control of metastatic disease. Sherman, Bonebrake, and Allen have utilized colloidal radioactive gold for injection into the parametrial zones of the uterus through the vagina, much like the insertion of radium needles into the parametrium. The results of their studies indicate that the use of radioactive gold, as a supplementary treatment for carcinoma of the cervix and vulva, is justified as an adjunct to the present methods of radiation treatment in these diseases. Flocks, Kerr, and co-workers have inserted Au^{198} into moderately advanced carcinomas of the prostate, not operable but showing no widespread primary lesions or distant metastases. Their reports indicate that there is some value in this form of treatment, but further evaluation is awaited. Preliminary

studies, in patients with pleural effusion or ascites resulting from metastatic cancer, have demonstrated that the local, intrapleural, or intraperitoneal injection of radioactive colloidal gold will sharply reduce the rate of formation of pleural fluid or ascites in some patients. Moses and associates have noted that complete cessation or marked retardation of fluid formation followed the intracavity injection of gold (Au^{198}) in approximately one-half of one hundred sixty-three patients with metastatic carcinoma and pleural effusion or ascites. They concluded, however, that while radioactive gold is useful, it is far from ideal in the therapeutic management of pleural effusions or ascites. The empirical dosage of Au^{198} based on clinical response is about 100 mc., but will vary considerably in individual cases. In some of the patients more than one injection of gold may be given in the presence of the reaccumulation of fluid. The technique of administration and dosage should be left to those qualified to give radioisotopes.

GENERAL MEDICAL SUPPORTIVE MEASURES

Before the advent of chemotherapy, endocrine therapy, and the application of radioisotopes, medical measures had held an important position in the care of the patient. The medical aspects of treatment have now assumed even greater importance in those individuals where the tumor is inoperable or has become generalized, requiring palliation. Cachexia anemia, and general debility require immediate correction, if possible, through rectifying the fluid and electrolyte balance, giving of transfusions, intranasal tube feeding, parenteral feeding, increased vitamin intake, etc. The relief of pain often does much for the patient's well-being. General medical palliation may include simply prescribing aspirin tablets or giving other nonnarcotic compounds such as Thorazine. If one finds that narcotics are necessary, a judicious attitude must be adopted, making every effort to avoid massive dosages to gain immediate relief. (Trial of drug combinations with small dosages may bring about adequate synergistic action with relief of pain.) The adverse synergistic effects of certain drugs must be taken into account. The more effective opiates in larger doses should be reserved for terminal cases with intractable pain. In using general medical measures for relief of pain, the specific forms of therapy discussed above should be considered and tried in appropriate cases. Addiction to narcotics can largely be avoided by the judicious use of chemotherapy, hormone therapy, irradiation therapy, and/or surgical measures.

The entire problem of palliation is an individial one for every patient, and requires a careful appraisal of the attitudes, both of the patient and the family. Sympathy for the patient and his problem, with a spirit of optimism, may serve to brace his morale and give him the lift upon which he may thrive from day to day. Whether a patient knows he has a malignant disease is not important. The vital question for the physician to answer is: has he conveyed a feeling of optimism to the patient about what he can do and is doing for him? The families of such patients must be thoroughly briefed and an air of courage and enthusiasm instilled into their demeanor. A listless, moping family spreads an aura of defeat and hopelessness. In this atmosphere a patient sinks in a mire of depression. The treatment during the terminal stages deserves the same kind, optimistic attitude, using hospitalization when necessary, but with the utilization of adequate home care where possible.

Bluestone points out that home care of the sick goes back to the dawn of time. Hospital or institutional care is of more recent origin and came about for reasons of home surroundings which made hospitalization desirable. Under this latter policy the family has shared little of the responsibility of the care of the patient. The hospital subsequently has developed a high degree of selectivity and exclusiveness which strains public relations. The Montefiore Hospital, New York City, in January, 1947, developed a Home Care plan which is catching on all over the country. It has returned the possibilities of home care, in relation to hospital care, to a relatively favorable position and bids fair to lighten the load on hospital beds. There are now some 30-odd Home Care programs, more or less complete, in the United States, with many more being considered, in addition to home care aid by individual agencies, such as the American Cancer Society, Visiting Nurse Associations, etc. Home Care programs as permanent, organized, extramural functions of hospitals must provide for the full participation of the family physician in every respect. Experience with properly conducted programs has thus far proved that the cost of extramural care on a comparative basis is about one-fourth that of hospital care.

VOL.
4
1956

In 1949, the Alexander and Margaret Stewart Trust made available appropriate monies for the organization of Home Care programs for cancer patients in the Washington area. The Georgetown University Hospital was fortunate in obtaining a grant from this fund in 1950 for the purpose of setting up a Home Care Cancer program. The Home Care service has been utilized far beyond our hopes, both by clinic patients and by private family physicians and their patients. The grant permits a load of twenty Home Care patients at any one time with the possibility that one bed in the hospital may be utilized 365 days a year.

It seems pertinent to set down a summary of the organization used at the Georgetown University Hospital, for, in my opinion, it fills a need of vast importance which any hospital or community faces in the care of the terminal or incurable cancer patient.

GEORGETOWN UNIVERSITY MEDICAL CENTER

Home Care Program for Cancer Patients

The plan provides adequate medical care for chronic cancer patients of the city in a manner which is most economical both to the patient and to the community and includes:

1. Using a minimum of expensive hospital care.
2. Securing maximum help from each patient's family.
3. Using all currently available facilities and avoiding duplication.
4. Applicability to all chronic cancer patients.

Each indigent chronic cancer patient must first be thoroughly studied in the hospital to determine his prognosis and the treatment which may be necessary. The patient is then placed on the roster of the Home Care physician and social worker, who will guide his care thereafter. As soon as all preparations are made and the patient is deemed ready, the patient is transferred to his home. Such patients will *not* be discharged from the hospital, but the hospital or clinic record will be continued as if a hospital admission. The Home Care physician, visiting nurse, and social worker visit the patient at home as required and furnish those items required for his or her care. If and when general hospital care is required, the case is "transferred" back to the hospital.

Services at home are supplemented by a hospital visiting nurse which his private physician or Home Care physician supervises. The nurse is invaluable for giving the family instruction and advice in the nursing care of the patient.

The social worker is the hub of the program, determining the needs of each patient as well as the adequacy of his home. She must know each family and obtain a maximum of aid from each member of the family. She must be the doctor's right arm without taking over his prerogative. She must be on best terms with all existing welfare organizations and cooperate, but not compete with them.

Any family physician may request aid for private patients by applying through the hospital Home Care secretary. If deemed an incurable cancer case after adequate diagnostic study, the patient may then be transferred to the Home Care Service. The Home Care physician will then care for the patient in cooperation with the family physician, being under the latter's direction rather than that of the hospital staff. However, in each such instance, the family is charged for the cost of the patient's care or that portion of the cost which seems a fair share. This service is limited to family physicians and is *not* available to specialists for private patients, although specialists may use the service through referral to a general practitioner.

VOL. 4 1956

Dr. Thomas Parran cites the Conference held in 1954 by the Commission on Chronic Diseases which set up the following objectives:

1. To identify the requirements of the long-term patient in the various stages and severity of illness.
2. To examine existing methods of providing care, explore new methods, and to enumerate principles which should govern medical charges.
3. To suggest patterns for desirable relations between services, facilities, and programs.
4. To recommend ways in which the financing of long-term care could be improved.

At this Conference emphasis was placed on the care of the long-term patient in his home, the relations of home care programs to the special hospital, the nursing home, and to other institutions, and the integration of services and facilities for long-term care.

The chronically ill in this country have been estimated at 5,300,000 (Parran) of whom 4,000,000 or 80 per cent are not in an institution. Medical hospital care currently is geared largely to patients with relatively acute illnesses. When home care programs, supported by private or public funds, are enhanced to cover wide fields of chronic illness, and adjusted to hospital facilities, they will obviate the present dilemma of the physician in caring for middle-and-lower-income-bracket patients with incurable and crippling disease.

SUMMARY

1. The magnitude of the problem of caring for inoperable and incurable, recrudescent cancer patients has been emphasized.

2. Many disciplines which have contributed to palliation, including chemotherapeutic, endocrinologic, surgical, radiotherapeutic, and general medical supportive measures, have been evaluated and discussed.

3. The usefulness and benefits of the palliative procedures have been pointed out.

4. The Home Care Cancer program at the Georgetown University Hospital has been outlined and recommended as an important adjunct to the care of the incurable cancer patient, with some thoughts on the care of the chronically ill.

5. No attempt has been made to cover many of the individual therapeutic techniques in detail.

REFERENCES

Adair, F. E., and Herrmann, J. B.: The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast, Ann. Surg. **123**:1023, 1946.

Adair, F. E., Treves, N., Farrow, J. H., and Scharnagel, I. M.: Clinical Effects of Surgical and X-Ray Castration in Mammary Cancer, J. A. M. A. **128**:161, 1945.

Alpert, L. K., Greenspan, E. M., and Peterson, S. S.: The Treatment of the Lymphomas and Other Neoplastic Diseases With Nitrogen Mustard, Ann. Int. Med. **32**:393, 1950.

Barnard, R. D.: Urethane in Anaplastic Carcinoma, J. A. M. A. **135**:450, 1947.

Bateman, J. C.: Cancer Chemotherapy, M. Ann. District of Columbia **24**:55, 1955.

Bateman, J., Klopp, C. T. and Cromer, J. K.: Hematologic Effects of Regional Nitrogen Mustard Therapy, Blood **6**:26, 1951.

Bergenstal, D. M., and Huggins, C.: Bilateral Adrenalectomy in Advanced Carcinoma, Proc. of the Second National Cancer Conference I, 353, 1952, Am. Ca. Soc., Inc., N. Y., 1954.

Berman, L., and Axelrod, A. R.: Urethane: Clinical, Hematologic and Histologic Observations on Patients With Malignant Disease, Am. J. Clin. Path. **18**:104, 1948.

Block, M., Spurr, C. L., Jacobson, L. O. and Smith, T. R.: Histopathologic Effects of Nitrogen Mustard Therapy Upon Normal and Neoplastic Hematopoietic Tissues, Am. J. Clin. Path. **18**:671, 1948.

Bluestone, E. M.: The Principles and Practice of Home Care, J. A. M. A. **155**:1379, 1954.

Borak, J.: Analgesic Effects of Roentgen Rays With Special Considerations of Bone Metastases of Cancer, Radiology **14**:328, 1930.

Bouchard, J.: Skeletal Metastasis in Cancer of the Breast; Study of Character, Incidence and Response to Roentgen Therapy, Am. J. Roentgenol. and Radium Therapy **54**:156, 1945.

Boyland, E., Clegg, J. W., Koller, P. C., Rhoden, E., and Warwick, O. H.: The Effects of Chloroethylamines on Tumors, With Special Reference to Bronchogenic Carcinoma, Brit. J. Cancer **2**:17, 1948.

Brendler, H., Chase, W. E., and Scott, W. W.: Prostatic Cancer; Further Investigation of Hormonal Relationships, Arch. Surg. **61**:433, 1950.

Bross, D. J.: Statistical Analysis of Clinical Results From 6-Mercaptopurine, Ann. N. Y. Acad. Sc. **60**:369, 1954.

Burchenal, J. H., et al.: Clinical Evaluation of a New Anti-Metabolite 6-Mercaptopurine in the Treatment of Leukemias and Allied Diseases, Blood **8**:965, 1953.

Burchenal, J. H., et al.: Clinical Studies on 6-Mercaptopurine, Ann. N. Y. Acad. Sc. **60**:359, 1954.

Burchenal, J. H., Burchenal, J. R., Kushida, M. W., Johnston, S. F., and Williams, B. S.: Studies on the Chemotherapy of Leukemia: II. The Effect of 4-Amino-Pteroylglutamic Acid and 4-Amino-N^{10}-Methyl-Pteroylglutamic Acid on Transplanted Mouse Leukemia, Cancer **2**:113, 1949.

Burchenal, J. H., Myers, W. P. L., Craver, L. F., and Karnofsky, D. A.: The Nitrogen Mustards in the Treatment of Leukemia, Cancer **2**:1, 1949.

Cade, S.: Chemotherapy in the Treatment of Malignant Disease, Brit. M. J. **2**:1193, 1949.

Campbell, J. H., and Cummins, S. D.: Metastases, Simulating Mammary Cancer in Prostatic Carcinoma Under Estrogenic Therapy, Cancer **4**:303, 1951.

Carroll, G., and Brennan, R. V.: Endocrine Therapy in Carcinoma of the Prostate, J. A. M. A. **157**:581, 1955.

Chamberlain, R. H.: Radiation Therapy in Cancer, Proc. of Second National Cancer Conference I, 40, 1952, Am. Ca. Soc., Inc., N. Y., 1954.

Clark, R. L., Jr.: Selection of Treatment in Advanced Carcinoma of the Rectum, South. M. J. **41**:765, 1948.

Clark, R. L., Jr.: The Present Status of Cancer Therapy, Postgrad. Med. **6**:89, 1949.

Coleman, C. C., et al.: Neurosurgical Methods for the Relief of Severe Intractable Pain, Virginia M. Month. **79**:422, 1952.

Colston, J. A. C., and Brendler, H.: Endocrine Therapy in Carcinoma of the Prostate: Preparation of Patients for Radical Perineal Prostatectomy, J. A. M. A. **134**:848, 1947.

Copeland, M. M.: Evaluation of Radioactive Isotopes as an Adjunct to Surgical Diagnosis and Therapy, J. Bone & Joint Surg. **33**:1021, 1951.

Copeland, M. M., Mattson, R. P., and Hiken, L. L.: Bone Metastases and Their Treatment, a Preliminary Report, Georgetown University Bull. **7**:76, 1954.

Craver, L. F.: Recent Advances in the Treatment of Lymphomas, Leukemias and Allied Disorders, Bull. New York Acad. Med. **24**:3, 1948.

Craver, L. F.: Recent Advances in Treatment of Inoperable Cancer, Bull. New York Acad. Med. **28**:385, 1952.

Craver, L. F.: The Nitrogen Mustards: Clinical Use, Radiology **50**:486, 1948.
Daland, E. M.: Palliative Treatment of Patient With Advanced Cancer, J. A. M. A. **136**:391, 1948.
Dameshek, W.: Chemotherapy of "Lymphoma" and Leukemia, Bull. New England M. Center **11**:49, 1949.
Demaree, E. W.: Local Recurrence Following Surgery for Cancer of the Breast, Ann. Surg. **134**:863, 1951.
Duncan, G. H.: Treatment of Prostatic Carcinoma by Oestradiol and Diethylstilbestrol, Brit. M. J. **2**:137, 1943.
Emmett, J. L., and Greene, L. F.: Bilateral Orchiectomy for Carcinoma of the Prostate gland; Clinical Experience, J. A. M. A. **127**:63, 1945.
Escher, G. C., Heber, J. H., Woodward, H. Q., Farrow, J. H., and Adair, F. E.: Newer Steroids in the Treatment of Advanced Mammary Carcinoma, Symposium on Steroids in Experimental and Clinical Practice, New York, 1951, The Blakiston Co.
Farber, S.: Some Observations on the Effect of Folic Acid Antagonists on Acute Leukemia and Other Forms of Incurable Cancer, Blood **4**:160, 1949.
Farber, S., et al.: Clinical Studies on the Carcinolytic Action of Triethylenephosphoramide Cancer **6**:135, 1953.
Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., and Wolff, J. A.: Temporary Remissions in Acute Leukemia in Children Produced by the Folic Acid Antagonist, 4-Amino-Pteroyl-Glutamic Acid (Aminopterin), New England J. Med. **238**:787, 1948.
Farrow, J. H.: Effect of Sex Hormones on Skeletal Metastases From Breast Cancer, Surgery **16**:141, 1944.
Farrow, J. H., and Adair, F. E.: Effect of Orchiectomy on Skeletal Metastases From Cancer of the Male Breast, Science **95**:654, 1942.
Fels, E.: Effects of Sex Hormones on Skeletal Metastases From Breast Cancer, Surgery **16**:141, 1944.
Fitzgerald, P. J., Foot, F. W., and Hill, R. F.: Concentration of I^{131} in Thyroid Cancer; a Study of 100 Consecutive Cases Showing the Relation of Histological Structure to the Function of Thyroid Carcinoma, Cancer **3**:86, 1950.
Flocks, R.: The Treatment of Carcinoma of the Prostate, Tr. West. Sect. Am. Urol. A. **19**:29, 1952.
Ford, J. C., and Drew, J. E.: Advising Radical Surgery—A Problem in Medical Morality, J. A. M. A. **151**:711, 1953.
Freeman, W.: The Non-Surgical Prolongation of Life, Postgrad. Med. **13**:473, 1953.
Freid, J., Goldberg, H., and Herrmann, J.: Treatment of Metastases From Cancer of the Breast, Am. J. Roentgenol. **63**:312, 1950.
Gellhorn, A.: Chemotherapy, the Physiopathology of Cancer, New York, 1953. Editors, Hamburger, F., and Fishman, W. H., Paul B. Hoeber, Inc. (Harper Bros.), pp. 854-919.
Gellhorn, A.: Clinical Cancer Chemotherapy, Proc. of Second National Cancer Conference I: 24, 1952, Am. Ca. Soc., Inc., N. Y., 1954.
Gellhorn, A., and Jones, L. O.: Chemotherapy of Malignant Disease, Am. J. Med. **6**:188, 1949.
Geschickter, C. F., and Copeland, M. M.: Radioisotopes, General Considerations, Atomic Medicine, Baltimore, 1953, edited by Behrens, C. F., The Williams & Wilkins Co., pp. 400-417.
ibid: Radiophosphorus and Radioiodine, Atomic Medicine, pp. 418-448.
ibid: Radioisotopes of Medical Interest, etc., Atomic Medicine, pp. 449-506.
Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, (3 ed.), Philadelphia, 1949, J. B. Lippincott Co., p. 472.
Godwin, J. T., and Escher, G. C.: Hormone-Treated Primary Operable Breast Carcinoma: A Pathological Study of 33 Cases, Cancer **4**:136, 1951.
Granger, G. A.: Non-Orthodox Cancer Remedies, M. Ann. District of Columbia, **24**:73, 1955.
Guiss, L. W.: The Role of Surgery in the Palliative Management of Inoperable and Recurrent Mammary Cancer, Proc. of the Second National Cancer Conference I: 259, 1952, Am. Ca. Soc., Inc., N. Y., 1954.
Gutman, A. B.: Tumors of the Skeletal System; Medical Aspects, Bull. New York Acad. Med. **23**:512, 1947.
Haddow, A., and Sexton, W. A.: Influence of Carbamic Esters (Urethanes) on Experimental Animal Tumors, Nature **157**:500, 1946.
Hall, B. E., Richards, M. D., Willett, F. M., and Feichtmeir, T. V.: Clinical Experience With 6-Mercaptopurine in Human Neoplasia, Ann. N. Y. Acad. Sciences, **60**:374, 1954.
Hare, H. F.: Radiation Treatment of Carcinoma of the Thyroid, Am. J. Roentgenol. **46**:451, 1941.
Hare, H. F., et al.: Observations on Rotational Therapy With Two Million Volt Roentgen Rays, J. A. M. A. **154**:890, 1954.
Harrington, W. J., and Moloney, W. C.: Treatment of Multiple Myeloma With Urethane, Cancer **3**:253, 1950.
Herrmann, J. B.: The Effect of Hormonal Imbalance on Advanced Carcinoma of the Male Breast, Ann. Surg. **133**:191, 1951.

VOL. 4 1956

Herrmann, J. B., and Adair, F. E.: Effect of Testosterone Propionate on Carcinoma of the Female Breast With Soft Tissue Metastases, J. Clin. Endocrinol. **6**:769, 1946.
Herrmann, J. B., Adair, F. E., and Woodard, H. Q.: Use of Testosterone Propionate in Treatment of Advanced Carcinoma of the Breast; Treatment of Osseous Metastases, Surgery **22**:101, 1947.
Hertz, R.: Administration of Massive Dosage of Estrogen to Breast and Prostate Cancer Patients: Blood Levels Attained, Proceedings of the Second National Cancer Conference, I: 282, 1952, Am. Ca. Soc., Inc., N. Y., 1954.
Horsley, G. W.: Surgical Castration in the Management of Carcinoma of the Mammary Gland, Proc. of the Second National Cancer Conference I: 261, 1952, Am. Ca. Soc., Inc., N. Y., 1954.
Howard, R. R., and Grosjean, W. A.: Bilateral Mammary Carcinoma in the Male Coincident With Prolonged Stilbesterol Therapy, Surgery **25**:300, 1949.
Hubeny, M. J., and Mass, M.: Roentgenologic Aspects of Metastases, Radiology **35**:315, 1940.
Huggins, C.: A Summary of Endocrine Effects in Advanced Prostatic Cancer, New York J. Med. **43**:519, 1943.
Huggins, C.: Endocrine Control of Prostatic Cancer, Science **97**:541, 1943.
Huggins, C.: Prostate Cancer Treated by Orchiectomy; 5-Year Results, J. A. M. A. **131**:576, 1946.
Huggins, C.: The Diagnosis of Cancer of the Prostate Including the Interpretation of Serum Phosphatase Values, Bull. New York Acad. Med. **19**:195, 1943.
Huggins, C., and Dao, T. L-Y.: Adrenalectomy and Oopherectomy in Treatment of Advanced Carcinoma of the Breast, J. A. M. A. **151**:1388, 1953.
Huggins, C., and Hodges, C. V.: Studies on Prostatic Cancer: I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate, Cancer Research **1**:293, 1941.
Huggins, C., Stevens, R. E., Jr., and Hodges, C. V.: Studies on Prostatic Cancer: II. The Effects of Castration on Advanced Carcinoma of the Prostate Gland, Arch. Surg. **43**:209, 1941.
Hunt, H. B., and Butler, R. H.: Role of Radiation Castration in the Palliative Treatment of Metastatic and Recurrent Mammary Cancer, Proc. of the Second National Cancer Conference I: 263, 1952, Am. Ca. Soc., Inc., N. Y., 1954.
Huseby, R. A.: Estrogen Therapy in the Management of Malignant Advanced Breast Cancer, Am. Surgeon. **20**:112, 1954.
Jacobson, W., Levin, W. C., and Holt, G.: Observations on the Treatment of Acute Leukemias With Analogues of Folic Acid, J. Lab. & Clin. Med. **23**:1641, 1948.
Karnofsky, D. A.: Chemotherapy of Neoplastic Disease, New England J. Med. **239**: pp. 226, 260, and 299, 1948.
Karnofsky, D. A., Abelmann, W., Craver, L. F., and Burchenal, J. H.: The Use of the Nitrogen Mustards in the Palliative Treatment With Particular Reference to Bronchogenic Carcinoma, Cancer I: 634, 1948.
Karnofsky, D. A., and Burchenal, J. H.: Present Status of Clinical Cancer Chemotherapy, Am. J. Med. **8**:767, 1950.
Karnofsky D. A., Burchenal, J. H., and Escher, G. C.: Chemotherapy of Neoplastic Diseases, Med. Clin. N. Amer. **34**:439, 1950.
Karnofsky, D. A., et al: Triethylene Melamine in the Treatment of Neoplastic Disease. A Compound With Nitrogen Mustard-like Activity Suitable for Oral and Intravenous Use, A. M. A. Arch. Int. Med. **87**:477, 1951.
Karpat, R., and Kuehn, C. A.: Metastatic Lesions of Cancer of Male Breast Treated and Improved by Surgical Castration, Case Report, Urol. & Cutan. Rev. **52**:521, 1948.
Kennedy, B. J., and Aub, J. C.: The Therapeutic Indications for Nitrogen Mustards in Lymphoma, M. Clin. North America **33**:1301, 1949.
Kennedy, B. J., Nathanson, I. T., and Aub, J. C.: Ethyl Carbamate (Urethane) in the Treatment of Mycosis Fungoides, Cancer **3**:66, 1950.
Klopp, C. T.: The Treatment of Cancer, M. Ann. District of Columbia, **21**:297, 1952.
Klopp, C. T., Alford, T. C., Bateman, J., Berry, G. N., and Winship, T.: Fractionated Intra-arterial Cancer Chemotherapy With Methyl-bis Amine Hydrochloride; a Preliminary Report, Ann. Surg. **132**:811, 1950.
Koenig, E. C., and Culver, G. J.: The Value of Roentgen Therapy in Carcinomatous Metastases to Bone, Radiology **41**:38, 1943.
Leucutia, T.: Value of Orchiectomy in the Treatment of Carcinoma of the Male Breast, Radiology **46**:441, 1946.
Loge, J. P., and Rundles, R. W.: Urethane (Ethyl Carbamate) Therapy in Multiple Myeloma, Blood **4**:201, 1949.
Lynch, J. P., Ware, P. F., and Gaensler, E. A.: Nitrogen Mustard in the Treatment of Inoperable Bronchogenic Carcinoma, Surgery **27**:368, 1950.
MacCarty, W. C., Jr.: Effects of Estrogenic Therapy on Metastases From Carcinoma of the Prostate, Radiology **49**:54, 1947.
MacDonald, I., and Guiss, L. W.: Clinical Symposium; Palliative Management of Carcinoma, California Med. **69**:144, 1948.

McGraw, A. B.: Breast Cancer, Testosterone Proprionate in Treatment of Recurrent Cancer, Arch. Surg. **57**:385, 1948.
McWhirter, R.: Carcinoma of the Breast, Brit. M. J. **2**:542, 1947.
ibid: Treatment of Cancer of the Breast by Simple Mastectomy and Roentgen Therapy, Arch. Surg. **59**:830, 1949.
Marinelli, L. D., Trunnell, J. B., Hill, R. F., and Foote, F. W.: Factors Involved in Experimental Therapy of Metastatic Thyroid Cancer With I^{131}; Preliminary Report, Radiology **51**:553, 1948.
Marshall, S., and Hare, H.: Carcinoma of the Breast; Results of Combined Treatment With Surgery and Roentgen Rays, Ann. Surg. **125**:688, 1947.
Morton, J. J.: Cancer Problem, J. A. M. A. **135**:957, 1947.
Moses, C., Kent, E., and Boatman, J. B., et al.: Experimental and Clinical Studies With Radioactive Colloidal Gold in the Therapy of Serous Effusions Arising From Cancer, Cancer **8**:417, 1955.
Motley, L.: Some Observations on the Use of Radioactive Isotopes in Therapy, Memphis M. J. **23**:135, 1948.
Nathanson, I. T.: Effect of Stilbestrol on Advanced Cancer of the Breast, Cancer Research **6**:484, 1946.
Nathanson, I. T., et al: Joint Meeting of Breast, Female Genital Tract, Genito-Urinary and Steroid Endocrinology Panels, Proc. of Second National Cancer Conference I: 145, 1952, Am. Ca. Soc., Inc., N. Y., 1954.
Nathanson, I. T., and Kelley, R. M.: Hormonal Treatment of Cancer, New England J. Med. **246**: pp. 135 and 180, 1952.
Nesbit, R. M., and Baum, W. C.: Endocrine Control of Prostatic Carcinoma, J. A. M. A. **146**:471, 1951.
Nesbit, R. M., and Baum, W. C.: Endocrine Control of Prostatic Carcinoma, Clinical and Statistical Survey of 1,818 Cases, J. A. M. A. **143**:1317, 1950.
Nesbit, R., and Cummings, R.: Prostatic Carcinoma Treated by Orchiectomy, J. A. M. A. **124**:80, 1944.
Osgood, E. E., and Chu, I. T.: The Effect of Urethane on the Nuclear Morphology of Cells of the Granulocyte Series as Observed in Marrow Cultures and Leukemic Blood, Blood **3**:911, 1948.
Pack, G. T., and Miller, T. R.: Combined Radiation Therapy and Surgical Treatment of Technically Inoperable Cancer, Radiology **57**:529, 1951.
Pack, G. T.: Argument for Radicalism in Cancer Surgery, Am. Surgeon **17**:271, 1951.
Parran, T.: New Paths to a Growing Problem, New England J. Med. **251**:287, 1954.
Paterson, E., Haddow, A., Ap Thomas, I., and Watkinson, J. M.: Leukemia Treated With Urethane, Compared With Deep X-ray Therapy, Lancet **1**:677, 1946.
Patten, W. B.: Surgical Treatment of the Pain of Malignancy, J. M. A. Alabama **23**:1, 1953.
Payne, J. T.: Surgery as Palliation in the Terminal Malignant Patient, Am. Surgeon **19**:924, 1953.
Rawson, R. W., Rall, J. E., and Peacock, W.: Limitations and Indications in the Treatment of Cancer of the Thyroid With Radioactive Iodine, J. Clin. Endocrinol. **11**:1128, 1951.
Rhoades, C. P.: Rational Cancer Chemotherapy, Science **119**:77, 1954.
Ritvo, M., and Peterson, O. S., Jr.: Regression of Bone Metastases From Breast Cancer After Ovarian Sterilization, Am. J. Roentgenol. **51**:220, 1944.
Rundles, R. W., Dillon, M. L., and Dillon, E. S.: Multiple Myeloma: III. Effect of Urethane Therapy on Plasma Cell Growth, Abnormal Serum Protein Components and Bence-Jones Proteinuria, J. Clin. Invest. **29**:1243, 1950.
Rundles, R. W., Dillon, M. L., Dillon, E. S., and Armstrong, J.: Effect of Urethane (Ethyl Carbamate) in Multiple Myeloma, J. Clin. Invest. **28**:807, 1949.
Rundles, R. W., and Reenes, R. J.: Multiple Myeloma: II. Variability of Roentgen Appearance and Effect of Urethane on Skeletal Disease, Am. J. Roentgenol. **64**:799, 1950.
Schilling, A., and Laszlo, D.: The Effect of Diethylstilbestrol on the Calcium, Phosphorus and Nitrogen Metabolism of Prostatic Carcinoma, J. Clin. Invest. **29**:918, 1950.
Seidlin, S. M., Marinelli, L. D., and Oshry, E.: Radioactive Iodine Therapy; Effect on Functioning Metastases of Adenocarcinoma of the Thyroid, J. A. M. A. **132**:838, 1946.
Sheppard, C. W., Goodell, J. P. B., and Hahn, P. F.: Colloidal Gold Containing the Radioistope Au^{198} in the Selective Internal Radiation Therapy of Diseases of the Lymphoid System, J. Lab. & Clin. Med. **32**:1437, 1947.
Sheppard, C. W., Wells, E. B., Hahn, P. F., and Goodell, J. P. B.: Studies of the Distribution of Intravenously Administered Colloidal Salts of Manganese Dioxide and Gold in Human Beings and Dogs Using Radioactive Isotopes, J. Lab. & Clin. Med. **32**:274, 1947.
Skinner, E. F., Carr, D., and Denman, W. E.: The Treatment of Inoperable Bronchiogenic Carcinoma With Methyl-bis, J. Thoracic Surg. **17**:428, 1948.
Smith, P. G., Rush, I. W., and Evans, A. T.: Preliminary Report on the Clinical Use of TACE (Chlorotrianisene) in Treatment of Prostatic Cancer, J. Urol. **65**:886, 1951.
Snider, G. E.: The Treatment of Boeck's Sarcoid With Nitrogen Mustard; Preliminary Report, South. M. J. **41**:11, 1948.

VOL
4
195

Spiller, W. G., and Martin, E.: Treatment of Persistant Pain of Organic Origin in Lower Part of Body by Division of Anterolateral Column of Spinal Cord, J. A. M. A. **58**:1489, 1912.
Spitz, S.: The Histological Effects of Nitrogen Mustards on Human Tumors and Tissues, Cancer **1**:383, 1948.
Steiner, P. E.: An Evaluation of the Cancer Problem, Cancer Res. **12**:445, 1952.
Stetten, D. W., and Weinberger, H. A.: Successful Progressive Massive Resection of Small and Large Bowel for Mesenteric Carcinomatous Metastases, Ann. Surg. **136**:326, 1952.
Sullivan, J. J., and Hartwig, C. H.: Use of Estrogen Therapy Preliminary to Radical Perineal Prostatoseminal Vesiculectomy in Carcinoma of the Prostate, Tr. West. Sect. Am. Urol. A. **19**:107, 1952.
Sutherland, A.: Psychological Impact of Cancer Surgery, Public Health Reports, **67**:1139, 1953.
Taylor, S. G., III, Hass, G. M., Crumrine, J. L., and Slaughter, D. P.: Toxic Reactions of 4-Aminopteroylglutamic Acid Aminopterin in Patients With Far-Advanced Neoplastic Disease, Cancer **3**:493, 1950.
Taylor, S. G., III, et al.: Effect of Sex Hormones on Advanced Carcinoma of the Breast, Cancer **1**:604, 1948.
Treves, N.: Castration as a Therapeutic Measure in Cancer of the Male Breast, Cancer **2**:191, 1949.
Trump, J. G., et al.: Two Million Volt Roentgen Therapy Using Rotation, Am. J. Roentgenol. **66**:613, 1951.
West, C. D., et al.: The Effect of Bilateral Adrenalectomy Upon Neoplastic Disease in Man, Cancer **5**:1009, 1952.
Wintrobe, M. M., and Huguley, C. M., Jr.: Nitrogen-Mustard Therapy for Hodgkin's Disease, Lymphosarcoma, the Leukemias and Other Disorders, Cancer **1**:357, 1948.

OL.
4
956

Additional References

Galton, D. A. G.: Chronic Myeloid Leukaemia. I. Some Observations on Chronic Myeloid Leukaemia, Brit. J. Radiol. **26**:285, 1953.
Galton, D. A. G.: Myleran in Chronic Myeloid Leukaemia; Results of Treatment, Lancet **1**:208, 1953.
Galton, D. A. G., and Till, M.: Myleran in Chronic Myeloid Leukemia, Lancet **1**:425, 1955.
Galton, D. A. G., and Timmis, G. M.: The Action of 1:4-Dimethanesulphonoxybutane in the Treatment of Chronic Myeloid Leukaemia. In Ogilvie, H., Ed.: British Empire Cancer Campaign; Twenty-ninth Annual Report Covering the Year 1951, London, 1952, British Empire Cancer Campaign, p. 37.
Haddow, A., and Timmis, G. M.: Bifunctional Sulphonic Acid Esters With Radiomimetic Activity, Acta, Union internat. contre cancer **7**:469, 1951.
Haddow, A., and Timmis, G. M.: Myleran in Chronic Myeloid Leukaemia; Chemical Constitution and Biological Action, Lancet **1**:207, 1953.
Herbst, W. P.: Histopathologic Studies in Prostatic Carcinoma Under Treatment by Castration, the Injection of Diethylstilbestrol or Both, Tr. Am. A. Genito-Urin. Surgeons **35**:337, 1942.
Herbst, W. P.: Thoughts and Observations on the Relation of Altered Hormonal Balance to Prostatic Malignancy, Urol. & Cutan. Rev. **46**:691, 1942.
Kerr, H. D., Flocks, R. H., Elkins, H. B., Culp, D., and Evans, T. C.: Follow-up Study of One Hundred Cases of Carcinoma of the Prostate Treated With Radioactive Gold, Radiology **64**:637, 1955.
Petrakis, N. L., Bierman, H. R., Kelly, K. H., White, L. P., and Shimkin, M. B.: The Effect of 1, 4-Dimethanesulfonyloxybutane (GT-41 or Myleran) Upon Leukemia, Cancer **7**:383, 1954.
Phillips, Ralph: The Indications for the Use of Supervoltage Irradiation, M. Ann., District of Columbia, **24**:535, 1955.
Shay, H., and Sun, D. C. H.: Clinical Studies of Triethylenethiophosphoramide in the Treatment of Inoperable Cancer, Cancer **8**:498, 1955.
Smith, N. J., Rosello, S., and Shay, H.: The Effect of Triethylenethiophosphoramide in the Treatment of Leukemia and Certain Lymphomas in Infants and Children, J. Pediat. **46**:493, 1955.
Wintrobe, M. M., Cartwright, G. E., Fessas, P., Haut, A., and Altman, S. J.: Chemotherapy of Leukemia, Hodgkin's Disease and Related Disorders, Ann. Int. Med. **41**:447, 1954.
Zarafonetis, C. J. D., Shay, H., and Sun, D. C. H.: Triethylenethiophosphoramide in the Treatment of Chronic Leukemia, Cancer **8**:512, 1955.

Editorials

REHABILITATION: BEING IS BELONGING

The focus of medicine is turning toward rehabilitation. Almost everybody is in favor of "rehabilitation," just as almost everyone can be counted upon to stand up in favor of the Golden Rule. When all is said and done, the definition of the Golden Rule and the way rehabilitation is to be accomplished probably will amount to the same thing. But the science of medicine expects doctors to have "good, sound, scientific" definitions for whatever they do. Sometimes I have the feeling that the workaday doctor has a tendency to shun, as being unscientific, any discussion of faith and of man's spirit in defining what he himself does and how patients respond. But the literature of medicine is thickly sprinkled with published reports on miraculous cures, drugs, and special treatment regimes which other doctors have failed to substantiate. These have a brief vogue and are forgotten. Usually it has turned out not to be the drug or the technique but the personality of the doctor, his belief in his treatment, and the patient's faith in the physician that has brought about the cure.

The road back to recovery from serious illness is rehabilitation. It is a highway with many byways, detours, and intersections, but it is a road without a terminus. It is a path that runs through the rest of a man's life. There are milestones along the way which the physician hopes the patient will reach; they are only points in an endless line. Whether a patient is recovering from a mental illness, a paralysis, an injury, or a coronary thrombosis, the process of rehabilitation is the same. Recovered patients commonly think back about their rehabilitative struggles, gaining strength to meet present difficulties from their partial mastery of that once precarious interlude. A man is made humble in serious illness, but his character is revealed in such a circumstance more than it is molded.

People concerned with patients sometimes speak of habilitation—not *re*habilitation—as if patients were being prepared and made ready for the first time. But it is never the first time, and each man faces anew each test of his strength not only with the power and courage he has nurtured in the past but with similar patterns of adaptation and adjustment. This he does not do alone. It is always in relationship to other people.

The expectations of doctors are not only of what they expect from themselves but what they expect from the patient. The doctor, prescribing a medication, expects it to work and to remedy the patient's illness. The expectation is antici-

Abstract of address presented at the Thirty-eighth Annual Conference of the American Occupational Therapy Association, San Francisco, Calif., Oct. 26, 1955. Opinions expressed in this paper are those of the author and are not to be construed as those of the Navy Department.

VOL
4
195

pation of the physician's power to cure. If the patient fails to measure up and to improve, as all "good" patients are supposed to do, the doctor may try another medicine or a different kind of therapy. In the end, if the patient does not get well, the doctor may feel a sense of impotence, depression, or defeat, or he may feel anger and resentment toward the patient who is so uncooperative as not to get well.

Is it possible to define rehabilitation at all, if it involves so many subtle factors? It was defined at a Washington conference as "the restoration of the [patient] to the fullest physical, mental, social, vocational, and economic usefulness of which [he is] capable." The rehabilitation road not only is an endless road: it is a fogbound one. No one could conceivably map out this road for another human being. It would be like trying to draw a detailed map of the world. Who knows what the fullest measure of any one of these factors is? Who knows what fullest usefulness means? And besides, usefulness for what? And who knows how capable a man is of reaching, for example, his "fullest social usefulness?"

The physical rehabilitation of a sick man is limited to the physical body recovery which drugs, surgery, and physical devices and means can accomplish. But the social and emotional factors in rehabilitation involve a man's spirit, and these may be the more essential factors. When asked what was the treatment for scarlet fever, someone once replied, "It depends on what's wrong with the patient."

Social rehabilitation means living: it means living together, and most important, living together satisfactorily. Some patients recover from serious bouts of tuberculosis able to live together with other sick people, but unable to live together satisfactorily with well people. Soon after leaving the sanatorium, they get sick again and return. Almost every sanatorium physician knows of patients who break down at the moment they are ready to be dismissed from the hospital, and this occurs over and over again. In mental illness, this is often why patients are ill in the first place, and they cannot get well until they can learn to live together satisfactorily.

In order to live together, emotional rehabilitation is essential. Emotions are feelings. Just being aware of feelings is not enough. The patient must understand his feelings. Yet merely understanding feelings is not enough. He must be able to cope with his feelings.

To know why one person becomes enraged or depressed is only a step on the journey. Finally, rehabilitation equates functioning, then functioning together, and ultimately the functioning nonpatient. At the point where Mr. Sick can live together with other people, cope with his own feelings, and function—work, love, and play—as a nonpatient, his rehabilitation has begun to take. His spirit, belief, and trust guide him when the physician is no longer there.

Only at such a point in recovery is he really being! and in being he is belonging. One simply cannot *be* alone. I mean really alone and really lonely. For not belonging is not being. To most people, not belonging is not being, and not being is nonexistence. It is a sort of death. And the wish to fall ill, or the wish to die, or the wish to remain ill is more common in those failing to recover than we

like to admit. Nothing seems so much alone as death. Nothing is so much together as living. This is why some people fear death, and those who believe death is not solitary but is a reunion often do not dread it, for to them it is not an ending.

When a man falls seriously ill, he usually broods about "what's happened to me." Then after he recovers from this shock, he wonders what other people will think. How will they feel? If he has a broken arm, he can be pretty sure what other people will think, provided he didn't break it doing something he shouldn't have been doing. If he has polio, he may think he knows what other people think, but he rarely will be right. If he has a contagious disease such as tuberculosis, he will be deeply concerned about what other people will think—and fear. If he has a mental disease he will be afraid of what other people will think, for he will remember his own illogical and irrational ideas about the mentally ill and recognize these attitudes in other people. It may strike him like a boomerang. The harder he threw it, the greater the force of its return.

The patient cannot "belong" if the people who are meaningful to him stand with their arms folded. Patients, like children, see through sham words, whether they come from family, friends, nurses, or doctors.

Being well and being sick are both a communal existence, which is why working with groups of patients instead of with one alone—that is, working with a diminutive community of people—is becoming increasingly important in rehabilitation. Here the sick help each other, and sometimes in more sophisticated and telling ways than the doctor or anyone else can do.

Rehabilitation in its crucial moments, when man's faith is tested, is like a blind landing. Recently I was a passenger in a plane which was to land at a fog-shrouded naval airfield: the ceiling was 500 feet. We landed by what is known as GCA, Ground Control Approach. I could hear the instructions through the earphones in my crash helmet. I had not even known before what GCA meant! But still I felt safe because the voice that brought us safely down to earth was comforting, sure, kind, and absolute. The pilot at the controls could not see the man on the ground, and the man on the ground could not see the plane or its occupants. The voice was saying, "If you cease to hear me, assume a communication defect and resume your flight pattern. Do not attempt to talk to me." It went calmly on: "You are now 5 miles from the runway and coming in nicely. Now you are 2 degrees to the left. . . there. . . that's fine. . . you're 50 feet high. . . good. . . you're 4 miles from the field now and coming in well. You're 3 degrees to the right. . . that's corrected now. . . you're 3 miles from the runway and doing well. . . you're 50 feet low. . . there. . . you're 1 mile from the runway and coming in perfectly. Now if you'll look down you'll see the field," and looking down from the cockpit, I could see the runway a hundred feet or so away, and we were speeding directly between the lights outlining its sides. This was bringing us to safety in a "scientific" manner, but the science was all carried through the spoken voice, and there was something about that voice that transcended the radar screens below. Those we took for granted: the voice was what was happening.

This, I believe, is a good analogy to rehabilitation. The patient, like the pilot, rehabilitates himself or lands safely, but in times of stress and crisis there

needs to be a human being to help, not to tell you what to do, because if you've got that far, you're expected to know how to operate, but to tell you when you're off course. In a sense, when I walked away from that plane I thought that reassuring, calm voice was like the voice of God. And perhaps that is our lot when another helps us—and really helps us to feel as if it couldn't have all been made to happen without another hand also at the controls. But this voice was human, and the voice was a caring voice because the owner of it cared. When life was at stake, the sense of belonging, the kinship with the voice heard in my helmet's earphones, meant being. It meant Being is Belonging.

HARRY A. WILMER, M.D., PH.D.*
Naval Medical Research Institute
Bethesda, Md.

---

*Commander, Medical Corps, United States Naval Reserve, U. S. Naval Hospital, Oakland, Calif. Assistant Clinical Professor of Psychiatry, Stanford University, San Francisco (on military leave.)

OL.
4
956

THE MANAGEMENT OF HYPERTHYROIDISM

Hyperthyroidism, untreated, may be a chronic and progressive disease, with symptoms maintained for twenty-five years and more. Such patients are seldom seen today. Treatment is usually instituted early in the course of the disease, although this is done more from fear of the acute manifestations and their consequences than because of concern over chronicity alone. Occasionally a patient with the disease enters remission spontaneously and without treatment.

It is now 130 and 120 years, respectively, since the early descriptions by Parry and Graves. The etiology and pathogenesis of the disease still remain obscure. Treatment designed to prevent or remove the underlying cause has therefore not been possible. Instead, therapy has been aimed at reducing the excessive output of secretion by the thyroid. Mechanical reduction in the mass of gland tissue has been the mainstay of therapy, and chemical block to hormonal synthesis by the gland has been its alternative. To accomplish the former, surgery, radioiodine, and external radiation are employed. To effect the latter, the antithyroid drugs, iodides, and certain anions such as thiocyanate and perchlorate have been given with varying degrees of ultimate success.

For the eye complications of the disease, radiation to the pituitary has been employed[1] and recently in one patient each, extirpation of the pituitary[2] and section of the pituitary stalk[3] have been performed.

With so many methods available, it is not surprising that disagreement as to the method of choice is widespread. However, what is surprising is the intensity of conviction with which the protagonists of one method often support this one over the others. Disagreement between experts is well illustrated in a recent volume on the subject[4]; the compromise point of view defined therein forms the basis for the present discussion.

In untreated hyperthyroidism, the results of treatment can be roughly quantitated. Remission follows subtotal thyroidectomy in about 90 per cent of patients. This figure, however, becomes 50 per cent or less when a second or third operation is performed for recurrence of disease subsequent to operation. Radioiodine is effective in almost all patients if the end result of hypothyroidism as well as euthyroidism is included. Prolonged antithyroid drug therapy is followed upon its cessation by sustained remission in about 70 to 80 per cent of selected patients, i.e., exclusive of toxic recurrent goiter, and usually of toxic diffuse goiter with both large glands and a severe grade of hyperthyroidism. However, in unselected series, the figure is nearer 40 to 50 per cent. External radiation therapy relieves no more than 50 to 70 per cent of patients. Thus operative intervention and radioiodine are the most efficient modalities of treatment.

Thyroidectomy entails certain complications, both specific for the procedure and nonspecific for surgical operations in general. The incidence of com-

VOL.
4
195

plications naturally varies with the skill of surgeon and anesthetist, and with the adequacy of preoperative preparation. Damage to the vocal cords and parathyroid glands, postoperative hemorrhage, often then with need for tracheotomy, and hypothyroidism are the most frequent of these and are seen in about 10 per cent of patients. Recurrence of the disorder at various intervals after the procedure also is seen in about 10 per cent. Thyroid storm and death postoperatively occur, but are very rare when preparation is adequate. On the favorable side, preparation for operation and relief from disease can be accomplished in a relatively short time with a reasonably reliable outcome for most patients. Also there is the knowledge that the future is essentially uncomplicated by late sequelae except for the occasional development of recurrence of hyperthyroidism, of onset of hypothyroidism, or of return of palpable but nonmalignant thyroid tissue.

Radioiodine is a medical therapeutic agent which is simply given by mouth. The dose may be followed after a day or two by antithyroid drugs in order to control the hyperthyroidism until the I^{-131} becomes effective. In general, the effects of a single dose are realized in about six to eight weeks, although occasionally not until four months have elapsed. With the use of antithyroid drugs, doses of I^{-131} can be given at intervals, as necessary, with the patient kept euthyroid for most of the time until permanent remission is achieved. There is suggestive evidence that the antithyroid drugs so used may increase the dosage requirement for I^{-131} if remission is to be achieved.[5]

The incidence of hypothyroidism, which varies from 7 to 25 per cent in different series, is the chief complication of the use of radioiodine. The parathyroid gland, gonads, and other tissues of the body are not known to be injured. However, the fear that radioiodine may give rise to late cancer twenty to twenty-five years after treatment is a constant handicap to the freer use of the method. Best opinion considers such an eventuality to be quite unlikely. So far no carcinogenesis has been reported although persistent changes in structure of the remnant of gland and in the cell nuclei have been described as late as five years after treatment.[6,7] Nevertheless, the more conservative advocates of radioiodine therapy believe that some caution in I^{-131} usage should be maintained. They propose that this modality is the one of choice for patients 40 to 45 years of age or older, but that surgery should be employed in the uncomplicated disease if the patient has not yet reached this age.

There are certain exceptions to this rule. When the life expectancy has been shortened by complicating disease, radioiodine can be given to younger patients and probably is the method of choice. I^{-131} is selected as the preferred method, even in younger age, when hyperthyroidism has recurred after previous operation, in view of the higher efficiency and lack of immediate risks of internal radiation compared to the poorer results from repeated operations.

The proper treatment for the patient with a small gland is still the subject of considerable debate. Many surgeons consider this type of patient to be unsatisfactory subjects for operation, whereas others see no contraindication to the procedure merely because of gland size. However, because this group of patients has the highest remission rate of all the groups treated by antithyroid

drugs or external radiation therapeusis, many favor the use of these methods for younger patients and choose radioiodine for older ones.

Patients with potential, or already existent, complicating severe infiltrative ophthalmopathy, especially older men, are often victims of progression of the eye complication following operation. In fact, progression may occur with any modality of treatment. However, as yet, the incidence of this complication after I^{-131} therapy given in small doses, and repeated as needed, has not been shown to exceed that of surgery and is probably the best method for these patients. Antithyroid drugs for early control over the hyperthyroidism, and thyroid by mouth to maintain euthyroidism and to prevent the onset of symptoms of hypothyroidism, can be given immediately after I^{-131}. Hypothyroidism seems definitely to predispose to flare-up in the eye symptoms. Antithyroid drugs are also commonly used alone, since dosage can be discontinued if necessary. However, the low ultimate remission rate from these agents must be taken into consideration.

Toxic nodular goiter is considered to be resistant to all methods of therapy by many experts in the field. Since the incidence of cancer is not greatly different from that in toxic diffuse goiter, the disease is often treated by the same rules as for the diffuse disease—operation for the younger and radioiodine for the older patients. However, if there is substernal extension of the goiter or tracheal compression and deviation, operation is preferable, since the gland may swell after I^{-131} therapy. Also when there is a question of malignancy, surgical exploration is advisable, if only for diagnostic reasons apart from treatment.

The management of juvenile hyperthyroidism has engendered opposing schools of thought. One school favors operation in view of the rapidity of recovery; the other favors chronic antithyroid drug therapy in view of the psychologic trauma associated with operation and in view of some evidence to the effect that the results are poorer in children than in adults.

Finally, the choice of treatment for the pregnant woman with hyperthyroidism is unsettled. The issue lies between operation or antithyroid drug therapy. Operation offers a more definitive result and permits nursing after delivery. There is some risk of disturbing the pregnancy. The antithyroid drugs, if used judiciously, can be given without danger of goiter in the child at birth, and obviate the risks of operation. However, the patient requires fairly close observation, and death of the newborn infant from goiter due to persistent overdosage of these drugs during pregnancy has occurred. Also, the drugs pass into the milk to reach the nursing young, thus prohibiting the mother from nursing her child. As the best compromise, many prefer operation in the first half of pregnancy, and antithyroid drugs if the patient has not been seen before the second half. Radioiodine passes through the placental barrier to reach the fetal thyroid and also enters the milk. It is therefore contraindicated throughout pregnancy and during the lactation period if the infant is nursing.

Procedures directed at the pituitary are too recent to be appraised without further confirmation. Moreover, there is a body of indirect evidence to suggest that hyperthyroidism is not maintained by the excessive secretion of a hyperactive pituitary,[8] so that procedures aimed at the hypophysis may have an element of nonspecificity about them, even if they prove to be effective. The

VOL. 4 1956

tendency for the eye changes to subside spontaneously must be remembered in appraising results. Finally, the consequences of panhypopituitarism are severe and must be weighted against the immediate gains for which such procedures are being contemplated.

It is recognized that the views just set forth represent a compromise which is not necessarily the same as that which might be made by others. Nonetheless, this outline provides a working basis for the treatment of hyperthyroidism and its variants, and, with few exceptions, treatment should be provided.

OL.
4
956

REFERENCES

1. Beierwaltes, W. H.: X-ray Treatment of Malignant Exophthalmos, J. Clin. Endocrinol. **13**:1090, 1953.
2. Albeaux-Fernet, M., Guiot, J., Braun, S., and Romani, J. D.: Results of Surgical Hypophysectomy in a Case of Malignant Edematous Exophthalmos, J. Clin. Endocrinol. **15**:1239, 1955.
3. Schneider, R. W., and Gardner, W. J.: Correction of Malignant Exophthalmos by Transection of the Pituitary Stalk After Unsuccessful Orbital Decompression, J. Clin. Endocrinol. **14**:830, 1954.
4. Werner, Sidney C., Editor: The Thyroid: A Fundamental and Clinical Text, New York, 1955, Paul B. Hoeber, Inc.
5. Werner, S. C.: Results in the Treatment of Hyperthyroidism With Radioiodine, I-131, Med. Clin. North America **36**:623, 1952.
6. Dobyns, B. M., and others: Functional and Histologic Effects of Therapeutic Doses of Radioactive Iodine on the Thyroid of Man, J. Clin. Endocrinol. **13**:548, 1953.
7. Werner, S. C., and Lattes, R.: Unpublished data.
8. Werner, S. C., Spooner, M., and Hamilton, H.: Further Evidence That Graves' Disease Is Hyperthyroidism and Not Hyperpituitarism: Effects of Triiodothyronine and Sodium Iodide, J. Clin. Endocrinol. **15**:715, 1955.

SIDNEY C. WERNER, M.D.
Department of Medicine
Columbia University
College of Physicians and Surgeons
New York, N.Y.

Books Received

SPLENIN A IN RHEUMATIC FEVER. By Alvin F. Coburn, M.D., Lucille V. Moore, M.D., Judith Wood, M.D., and Mary Roberts, R.N. Pp. 87; with 5 figures. Springfield, Illinois, 1955, Charles C Thomas.

SEXUAL HYGIENE AND PATHOLOGY. By John F. Oliven, M.D. Pp. 481; indexed. Philadelphia, 1955, J. B. Lippincott Company. Price $10.00.

ATLAS UND PRAKTIKUM DER DERMATOLOGIE UND VENEROLOGIE. Von Prof. Dr. med. W. Burckhardt. Pp. 279; indexed, with 156 figures. München und Berlin, 1955, Verlag von Urban & Schwarzenberg (in the United States, Intercontinental Medical Book Corporation, New York City). Price $11.50.

THE SELECTED PAPERS OF JOSEPH W. MOUNTIN. Sponsored by the Joseph W. Mountin Memorial Committee. Pp. 356; 1956. The American Public Health Association, 1790 Broadway, New York City, has agreed to make the volume available to those wishing to purchase it at a cost of $5.00.

SYMPOSIUM SUR LES DERMATOSES PROFESSIONNELLES. Societe Francaise de Dermatologie et de Syphiligraphie et Societes de Medecine du Travail de France. Pr. Claude Huriez, Secretaire General du Symposium. Cite Hospitaliere de Lille, 10-11 Juin, 1955. Masson & Cie, Paris, France.

INTRODUCTION TO VIROLOGY. By Gilbert Dalldorf, M.D. Pp. 102; indexed, with 6 6 figures. Springfield, Illinois, 1955, Charles C Thomas. Price $3.50.

MENTAL HEALTH PLANNING FOR SOCIAL ACTION. By George S. Stevenson, M.D., Sc.D. Pp. 358; indexed. New York, London, Toronto, 1956, The Blakiston Division, McGraw-Hill Book Company, Inc. Price $6.50.

SYMPOSIUM ON ATHEROSCLEROSIS. Irvine H. Page, M.D., Chairman. Pp. 249; indexed, with 54 figures. Washington, D. C., 1955, National Academy of Sciences—National Research Council Publication 338. Price $2.00.

VOL
4
195